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1. Bindler, R. L., et al., *Am. J. Med. Sci.*, 19:622, Apr., 1955; *J. Surg.*, 7: 14, and Zipes, Albert, *Circulation*, 9:39, Jan., 1954; 3. Nichol, E. S., in Conn, H. F., *Current Therapy 1954*, Philadelphia, W. B. Saunders Co., 1954, p. 193; 4. Jamison, W. L., et al., *Am. J. Med. Sci.*, 3:321, Aug., 1955; 5. Glauert, A. Ross, *Brit. Med. J.*, 2:321, Aug. 16, 1952.

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Editorial

Auditory and Visual Perception of Cardiac Vibrations

SINCE the discovery by Laënnec in 1816 that the sounds produced by the heart could be well heard through a "quire of paper rolled up into a sort of cylinder," physicians have availed themselves of this aspect of physical diagnosis. All manner of stethoscopes have been devised and used from the wooden monaural type to the present binaural stethoscope but there has been little improvement in the design of the stethoscope for 60 years.

In addition to the appreciation of sound by the ear, it was early noted that these same vibrations could be recorded on photographic paper—at first by mechanical devices such as the Franck capsule and more recently by electronic means—to produce visual records of the sounds. Such recordings are called stethograms or phonocardiograms. The earlier instruments suffered from poor frequency response, did not accurately reproduce the cardiac spectrum, and at the same time introduced certain artifacts. Owing to the great advances in electronics in the last 15 years it is now possible to obtain much more fidelity in records of the vibrations initiated by the beating heart.

With the introduction of magnetic tape recording after World War II, it has become possible to record easily and with fidelity these sounds and murmurs, so that they can be reproduced as they are heard through the stethoscope. An outgrowth of the special oscilloscopes developed during the war for radar scopes now makes it possible to visualize these vibrations produced by the heart at the same time that they are heard by the ear—a true audiovisual combination.

Each of these methods has its own particular usefulness, depending upon the information desired. For routine diagnosis and the teaching of auscultation it is our belief that the simultaneous auditory perception and visualization of the cardiac sounds is of the utmost importance. It is also essential that an adequate filter system be used to emphasize limited frequency ranges, so that faint murmurs can be accentuated without interference by loud sounds and murmurs in other frequency ranges. Permanent recordings on magnetic tape for future reference add greatly to the value of the method.

For certain types of research and for special diagnostic procedures it is necessary to make photographic recordings of the heart sounds and murmurs together with some other event in the cardiac cycle such as the electrocardiogram. Records of this type can be subjected to careful analysis for the timing of the events of the cardiac cycle. Examples of these events are the delay in the onset of the first heart sound in mitral stenosis and the prolongation of right ventricular systole in pure types of pulmonic stenosis without interventricular communications. It seems quite clear that more precise diagnostic information can be obtained from these various procedures but that they each have their own advantages and limitations; the thoughtful physician will select and use the combination most likely to give valid results in a given case.

Attention may be called to some of the advantages that result from the combined use of these methods. First, the simultaneous visualization and auditory perception of the sounds of

the heart have entirely changed our concept of the teaching of cardiac auscultation. Our group believes that we can now teach with confidence, in that the student is aware of and appreciates the more difficult auscultatory phenomena. This confidence has developed from the testing of a large number of physicians at different stages of training with "unknown" recordings on tape before and after different teaching methods. It has become clear that it is now possible, in even a few hours, to develop the auditory acuity of physicians in the perception of heart sounds in a way that we did not believe possible. It should now be relatively easy to advance the auscultatory ability of the senior medical student to the point he would formerly have reached after a residency in medicine and the resident can be advanced beyond the attending physicians.

Some other points in which advantages occur are the more precise diagnosis of valvular disease by the use of these methods. We are chagrined to admit that we have discovered a number of both clinic and private patients in whom mild to gross diagnostic errors were made until one of the methods mentioned above was incorporated into the routine physical examination. It is now our custom initially to examine all patients with an audiovisual recorder of some type.

Follow-up of cases is much more precise and often a "new" sound or murmur has been shown to have been present for some time on review of the previous tape recordings on the patient. The diagnosis of various types of congenital heart disease has improved considerably by the recognition of the pulmonary and aortic components of the second pulmonic sound and

the duration of murmurs in relation to these sounds. Many cases of mitral stenosis have been recognized because of the attention compelled by the recognition of the "opening snap" in mitral stenosis. Valuable information has been obtained by the correlation of preoperative and postoperative tape recordings of both congenital and rheumatic lesions. With further correlation it may be possible, in certain cases, to make accurate diagnoses without recourse to the expensive, time-consuming, and occasionally dangerous procedures of cardiac catheterization and angiocardiology.

We have been gratified at being able to correlate the auscultatory findings with the post-mortem anatomic findings, though at times this correlation or lack of correlation is disconcerting in the present state of our knowledge.

Attention should be called to the library of tape recordings of heart sounds and murmurs that has been developed by a committee of the American Heart Association for the furtherance of professional education. Information about these recordings may be obtained from the American Heart Association.*

In summary, many physicians are deficient in their ability to make accurate diagnoses of certain cardiac lesions by auscultation. The careful, thoughtful physician will probably realize this deficiency in himself and will constantly seek to improve his command of this art. It is hoped that more general use of the methods briefly mentioned in this short résumé may help him in reaching this goal.

J. SCOTT BUTTERWORTH

* American Heart Association, 44 East 23rd Street, New York, N. Y.



All the marvellous discoveries of recent times cannot remove the physician from his post of honour in detecting morbid phenomena and following the mysterious rhythm of life and death: a post, that is, at the bedside of the patient.—ARTURO CASTIGLIONI, 1874.

Aortic Aneurysm

Report of 101 Cases

By BROOKE ROBERTS, M.D., GORDON DANIELSON, M.D., AND WILLIAM S. BLAKEMORE, M.D.

An evaluation of the management of patients with aneurysm of the aorta seems timely because of new and promising methods of treatment. The risks of nonoperative and operative treatment are presented from the experiences with 101 patients admitted to the Hospital of the University of Pennsylvania during the years 1950 through 1955. Follow-up data indicate that the mortality of nonoperative treatment is considerably greater than that of excision of the lesion, in spite of the poor operative risk of many patients in this group. The nonoperative mortality within 1 year of diagnosis was approximately 50 per cent. Many of these patients died of rupture of the aneurysm.

RECENT developments in vascular surgery have focused attention on many lesions previously refractory to treatment. Among such conditions aneurysms of the aorta rank high. Sporadic attempts to correct these lesions by wrapping,^{1, 2} ligation,³ wiring,^{4, 5} and other methods⁶⁻⁸ had been reported; but, with few exceptions,⁹ the end results had not been encouraging. Since the introduction of grafts for replacement of major vessels, however, renewed interest¹⁰⁻¹³ has been given to aneurysms generally. To render rational judgments with regard to the problem presented by these patients, it is essential to know the natural history of these conditions, the prognosis both with and without treatment, and the prognosis for the various forms of treatment. For this reason the cases seen during the period from January 1950 to January 1956 at the Hospital of the University of Pennsylvania have been reviewed.

MATERIAL

During the 6 years from 1950 through 1955, 101 patients were admitted to the Hospital of the University of Pennsylvania in whom a diagnosis of aortic aneurysm was established. We have been able to follow all of these patients. During this period our approach to these lesions underwent a radical change. At first only symptomatic treatment was offered. The first excision of an aortic aneurysm in

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this hospital was in 1951 when a ruptured saccular abdominal aneurysm was successfully removed. In 1953 such an operation was again attempted, and since that time it has been done with increasing frequency. The operated patients have been followed for relatively short periods of time, inasmuch as they are concentrated in the later years of the study. Since the mortality has been high in the unoperated group and has usually occurred within a short time after the diagnosis was established, it appears that some valid comparison can be made between those who were subjected to surgery and those who were not.

The entire group of patients with aortic aneurysms has been divided into those with thoracic and those with abdominal aneurysms. Each group in turn has been subdivided into those who have been operated upon and those not subjected to surgery. The operative procedures were carried out by 6 surgeons.

RESULTS

Aneurysms of the Abdominal Aorta

Between January 1950 and January 1956, 65 patients with abdominal aortic aneurysms were admitted to the Hospital of the University of Pennsylvania. Only 3 of them had a positive serologic test for syphilis. In an additional 10 cases the test was not recorded, and the rest had negative tests. These figures strongly confirm the views of many authors^{4, 14, 15} that today the great majority of abdominal aneurysms arise on the basis of arteriosclerosis and not syphilis.

Of the 65 patients, 30 were subjected to operation. The reasons for not operating varied, and included refusal of operation by the patient. The usual reason, however, was the judgment of the physician that the risk of the

operation was too great or that the presence of other diseases made the operation unwarranted. During the last 3 years a much higher percentage of patients have been subjected to operation than during the first 3 years of the study.

Age and Mortality. Table 1 shows the ages of the patients with abdominal aneurysms and the mortality for the various age groups, both among the operated and nonoperated patients. The surgical mortality includes any patient who died within 30 days of operation. Of the patients who survived this period, all but 3 are still living. One patient whose aneurysm was wrapped with cellophane died 6 months later. The first patient whose aneurysm was excised died 44 months later of rupture of a new thoracic aneurysm, and the third patient died of a cerebrovascular accident 23 months after resection of the aneurysm.

Of the 15 nonoperated patients first seen in the year 1955, and therefore not followed for 1 year at the time of this writing, 8 have already died, 5 of them from rupture of the aneurysm.

The operative mortality (table 1) is based on all operations for abdominal aneurysms during the 6-year period, including 2 patients who were simply explored without execution of any definitive procedure. Both these patients died shortly after surgery. Their explorations were performed because of symptoms of "an acute abdomen" due to rupture of the aneurysm before grafts were available in our hospital. In 2 patients early in the series the aneurysms were wrapped with cellophane, and in the remaining 26 patients the aneurysms were excised. In 2 of these 26 patients, grafts were not required, 1 of the aneurysms being sacular, though not syphilitic, with a small neck that was closed directly. The second patient had such tortuous iliac vessels that after excision of the aneurysm an end-to-end anastomosis was accomplished when the iliac vessels were straightened out. Among the 26 patients in whom the lesion was excised, there were 8 operative deaths, or a mortality of 31 per cent. Four of these 8 deaths occurred in patients with ruptured aneurysms. If they were excluded, the operative mortality would be 18 per cent (4 of 22 patients). These residual 4

TABLE 1.—Abdominal Aortic Aneurysms—Sixty-five

Age	Total patients	Operative deaths	Total deaths within 1 year	Surviving	
				At end of 1 year	Followed less than 1 year
Operated					
30-39	1 (1)*	0 (0)	0 (0)	1 (1)	0 (0)
40-49	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
50-59	8 (1)	2 (1)	2 (1)	5 (0)	1 (0)
60-69	15 (3)	4 (2)	5 (2)	4 (1)	6 (0)
70-79	5 (3)	4 (3)	4 (3)	0 (0)	1 (0)
80-89	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	30 (8)	10 (6)	11 (6)	11 (2)	8 (0)
Unoperated					
30-39	0 (0)	— —	0 (0)	0 (0)	0 (0)
40-49	0 (0)	— —	0 (0)	0 (0)	0 (0)
50-59	4 (0)	— —	2 (0)	1 (0)	1 (0)
60-69	11 (4)	— —	6 (4)	3 (0)	2 (0)
70-79	17 (4)	— —	9 (4)	4 (0)	4 (0)
80-89	3 (0)	— —	2 (0)	1 (0)	0 (0)
	35 (8)		19 (8)	9 (0)	7 (0)

* Parentheses signify aneurysm ruptured or dissecting when first seen.

deaths were due to rupture of the graft at 28 days, pulmonary embolus, thrombosis of the graft, and cerebral hemorrhage 4 weeks post-operatively.

It is worth pointing out that the very high operative mortality of 80 per cent in the 70 to 79 age group is affected by the fact that 3 of the 4 patients who died had suffered rupture of the aneurysm prior to operation. In all, 8 cases of ruptured abdominal aneurysms were operated upon, and 6 of them died.

Of the entire group of patients, 16 had had a rupture of the aneurysm when first seen. Eight of these were subjected to operation, 8 were not. All the latter patients died, whereas 2 of the 8 subjected to surgery were saved. It is worth emphasizing that among the last 16 patients with unruptured aneurysms only 1 operative death occurred. The early cases therefore have greatly affected our mortality figures.

Approximately 40 per cent (11 of 27) of the patients who were not operated upon and who had not had a rupture of their lesion when

TABLE 2.—*Survival of Thirty-five Patients with Untreated Abdominal Aortic Aneurysms*

Year first seen	Patients seen in year	Patients living in January 1956
1950	2 (0)*	0 (0)
1951	4 (2)	1 (0)
1952	4 (0)	0 (0)
1953	3 (0)	1 (0)
1954	7 (3)	2 (0)
1955	15 (3)	7 (0)
	35 (8)	11 (0)

* Parentheses signify aneurysm ruptured or dissecting when first seen.

first seen died within 1 year. Six of these 11 patients died of ruptured aneurysm, and 5 of other causes. Of the 9 patients who survived 1 year, 5 have since died, 2 of them from rupture of the aneurysm. Two of these 5 patients died in the second year, 1 in the third, and 2 in the fourth year after the diagnosis was made. Of the 4 patients who are still living, 1 is in the third year, and in another 58 months have elapsed following the diagnosis.

Of the entire 35 nonoperated patients, 16 have died as a direct result of the aneurysm, 8 others from other causes. The short survivals of patients who were not treated by operation, even excluding those patients who had a ruptured or a dissecting lesion when first seen, indicate a grave prognosis (table 2).

Thus, the dismal picture reported in other series^{1, 16} is again apparent in our group. There was, however, a certain amount of selection in this group, particularly in the last few years: as a rule, the better risk patients were subjected to operation.

Aneurysms of Thoracic Aorta

During the same time 36 patients were seen with aneurysms of the thoracic aorta. In contrast to those with abdominal aneurysms, a test for syphilis was positive in 18 of the 36, negative in 12, and not recorded in 6 cases. That a higher proportion of thoracic aneurysms than abdominal aneurysms arise from syphilitic infection has long been recognized and is confirmed in our series.

Age and Mortality. Table 3 gives the ages and

TABLE 3.—*Thoracic Aortic Aneurysms—Thirty-six*

Age	Total patients	Operative deaths	Total deaths within 1 year	Surviving	
				At end of 1 year	Followed less than 1 year
Operated					
20-29	3 (0)	0 (0)	0 (0)	3 (0)	0 (0)
30-39	1 (0)	1 (0)	1 (0)	0 (0)	0 (0)
40-49	3 (0)	3 (0)	3 (0)	0 (0)	0 (0)
50-59	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)
60-69	2 (0)	1 (0)	1 (0)	1 (0)	0 (0)
70-79	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
80-89	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	10 (0)	5 (0)	6 (0)	4 (0)	0 (0)
Unoperated					
20-29	0 (0)	— —	0 (0)	0 (0)	0 (0)
30-39	2 (1)	— —	2 (1)	0 (0)	0 (0)
40-49	4 (0)	— —	3 (0)	1 (0)	0 (0)
50-59	5 (0)	— —	1 (0)	3 (0)	1 (0)
60-69	7 (2)	— —	5 (2)	2 (0)	0 (0)
70-79	7 (1)	— —	3 (1)	3 (0)	1 (0)
80-89	1 (0)	— —	0 (0)	1 (0)	0 (0)
	26 (4)		14 (4)	10 (0)	2 (0)

* Parentheses signify aneurysm ruptured or dissecting when first seen.

mortality of these patients and, as before, they are divided into those operated and not operated upon. Twenty of the 26 nonoperated patients were first seen more than a year before the end of this study, and 10 survived 1 year or more. Of the remaining 6 unoperated patients followed less than a year, 4 have died, 2 and possibly 3 of their aneurysm. Of the 10 patients who survived 1 or more years without operation, 6 are still alive; 4 are living in their second year, 1 is in his third, and the last patient is in his fourth year after the diagnosis was established. Of the remaining 4 that died, 3 died of ruptured aneurysm, and 1 of coronary occlusion. In contrast to these short survivals, aneurysms were present in 2 patients for 6 and 9 years respectively before their eventual death from rupture. Thus, of this group of 26 patients, a total of 18 have died, of which 9 and possibly 10 died of rupture or dissection.

When the mortality is tabulated with regard to the years followed, a relatively short survival

TABLE 4.—*Survival of Twenty-six Patients with Untreated Thoracic Aortic Aneurysms*

Year first seen	Patients seen in year	Patients living in January 1956
1950	3 (1)*	0 (0)
1951	0 (0)	0 (0)
1952	3 (0)	1 (0)
1953	4 (0)	1 (0)
1954	10 (2)	3 (0)
1955	6 (1)	2 (0)
	26 (4)	7 (0)

* Parentheses signify aneurysm ruptured or dissecting when first seen.

is again seen (table 4). The high operative mortality among the thoracic cases is apparent in table 3. Among the youngest group, 2 of the 3 patients had aneurysms associated with coarctation of the aorta. Such aneurysms are more favorable for resection. These patients have done well with resection and grafts. In 2 patients early in the study the lesions were wrapped with cellophane. One died 3 days later and the other 11 months later, both of rupture of the aneurysms. Attempts to excise 2 aneurysms of the arch were unsuccessful, and in several cases the surgeon believed that the lesion was too extensive to be resected after it was exposed. Of the 5 who survived operation 3 are living more than a year, and the other 2 died of rupture of the lesions. With the recent development of hypothermia and vascular shunts, it is reasonable to predict that more favorable results will be obtained in this group of patients.

Signs and Symptoms of Aortic Aneurysms

Sex. The sex incidence of the 101 cases showed 20 women and 81 men in the series. Fifty-two men and 13 women had abdominal aneurysms, while 29 men and 7 women had thoracic lesions. It is interesting that the women were usually considerably older than the men. The average of the women with abdominal aneurysms was 73 and the median age was 74; men on an average were 8 years younger, the median and average age both being 65 years. Among patients with thoracic lesions the ages were more nearly equal. The average for women

TABLE 5.—*Symptoms of Patients with Aortic Aneurysms*

Symptoms	Abdominal aneurysms	Thoracic aneurysms
None.....	16	13
Pain.....	38	19
Mass.....	12	—
Pulsation.....	5	—
GI disturbances.....	4	—
Dysphagia.....	—	1
Sense of pressure.....	—	1
Dyspnea.....	—	10
Cough.....	—	3
Duration of Symptoms		
Less than 30 days.....	15	6
1-6 months.....	21	5
6 months-1 year.....	4	1
1-2 years.....	4	2
2-3 years.....	1	2
3-4 years.....	—	4
Greater than 5 years.....	—	3

was 58 years, with a median of 55 years; the average age of men was 56 years with a median of 61 years. Of the women with thoracic lesions 5 of the 7 had syphilitic aneurysms, thus accounting for the younger age.

Hypertension. It is recognized that hypertension is often found with arteriosclerotic aneurysms.^{13, 14} If pressures over 150 systolic or 100 diastolic are regarded as hypertensive, 38 of the 65 patients with abdominal aneurysms, or 58 per cent, were hypertensive. This percentage is lower than that usually reported.^{13, 15} Among the patients with thoracic aneurysms, 22 (61 per cent) showed pressures above 150/100.

Symptoms. The symptoms of the patients with abdominal aneurysms are given in table 5. Ten of the 13 patients with ruptured abdominal aneurysms had symptoms less than 1 month prior to rupture. Most of these apparently did not have any premonitory symptoms. Pain, of course, was uniformly present at the time of rupture, but the absence of pain cannot be taken to mean that the lesion is "safe."

Pain, when present, was clearly the dominant symptom and was usually felt in the back or epigastric area, but occasionally was experienced in the region of the hip, or even the leg.

Among the patients with thoracic aneurysms, pain was again the dominant symptom (table 5). Here, however, additional symptoms arising

from the compression of structures lying within the thorax were noted. At times, it was difficult to be certain that the symptoms were directly related to the presence of the aneurysm, rather than to an accompanying disease. Among these patients were 3 with ruptured aneurysm and prior symptoms for less than 1 month.

A study of table 5 indicates that thoracic aneurysms are apt to give rise to symptoms earlier than abdominal lesions.

DISCUSSION

During the last half century a profound change in the relative incidence of thoracic and abdominal aortic aneurysms has apparently occurred. It has long been recognized that syphilis is a much more frequent etiologic factor in thoracic than in abdominal aneurysms; the reverse is true of arteriosclerosis. As the incidence of syphilis has decreased, one would expect a relative decrease in thoracic aneurysms. It would appear, however, that there also has been an absolute increase in aneurysms of the abdominal aorta, which may well be related, in part, to the increasing number of elderly people in our population. When Osler¹⁷ wrote of abdominal aneurysms in 1905, he reported only 16 cases in as many years at the Johns Hopkins Hospital, and referred to the reported autopsy series in Vienna in which only 3 of 222 aortic aneurysms involved the abdominal aorta. Kampmeier¹⁸ in 1936 reported that thoracic aneurysms were approximately 8 times more frequent than abdominal lesions at Charity Hospital in New Orleans; subsequent reports have shown that the ratio has gradually been reversed.¹⁹ In 1952 Maniglia and Gregory²⁰ in Philadelphia, reported abdominal aneurysms to be more than twice as frequent as thoracic aneurysms. The increase in vascular disease generally is being reflected in an increasing incidence of abdominal aneurysms. Today, these lesions are not rare, and the sex incidence in this series, namely, 4 males to 1 female, is not surprising in vascular disease.

Knowledge of the prognosis of these lesions is of the greatest importance in formulating a rational decision with regard to their treatment. It has generally been recognized that an aortic aneurysm constitutes a distinct threat to

life. The type and location of the lesion have some effect on its prognosis. Syphilitic aneurysms lie more proximal and generally have a poorer prognosis than arteriosclerotic lesions. Syphilitic abdominal aneurysms are more apt to extend above the renal arteries than the more common arteriosclerotic aneurysms^{10, 21} and thus have a poorer operative as well as non-operative prognosis. In our experience with arteriosclerotic aneurysms, the aorta has nearly always been of increased diameter throughout, even though the aneurysm itself starts below the level of the renal artery.

Whether or not symptoms arise from the aneurysm, does not permit one to predict the period remaining before rupture may occur. This has been pointed out by deTakats and Marshall¹ and others^{21, 22} and is confirmed in our series. One must not, therefore, think that the patient can be watched with safety if the lesion is asymptomatic.

Pain and erosion of the vertebrae are usually more prominent in syphilitic aneurysms. Today many asymptomatic abdominal aneurysms are being diagnosed, and the prognosis is better than previously when no therapy was of avail. In his study Crane²¹ found a rather close correlation between the likelihood of rupture and the size of abdominal aneurysms. Lesions that were at least 7 cm. wide had a far higher incidence of rupture than the smaller ones. This is apparently due to the fact that the distending force increases as the diameter of the lesion increases, and the wall becomes relatively weaker as it becomes progressively larger.²³ It follows that an aneurysm will usually distend to more than 7 cm. in diameter before rupturing. It is surprising that once these lesions begin to enlarge, they do not all go on to rupture in a brief time.

The prognosis of patients with abdominal aneurysms stated by Estes¹⁴ from the Mayo Clinic is borne out by most smaller series. Roughly one third of his patients died within a year after the diagnosis was made and four-fifths were dead within 5 years. Of those who died, approximately two-thirds died of rupture of the aneurysm. In Kampmeier's¹⁶ series of abdominal aneurysms, in which 57 per cent of the patients had syphilis, 2 out of 3 died in the

hospital during the admission in which the diagnosis was made. In the present series, more than 50 per cent of the unoperated patients with abdominal aneurysms were dead within a year; a little less than half of these deaths were the result of rupture of the lesion.

With excision of abdominal aneurysms the prognosis appears distinctly improved. It is our present belief that unless there is some strong contraindication to surgery, an abdominal aneurysm should be excised and replaced by a graft or prosthesis. Although the operative mortality from this procedure is still considerable, it is rapidly declining, and the risk is reasonable when weighed against the alternative of "letting nature take its course." We think that other surgical methods are not so satisfactory as excision; they have not been employed in preference to resection in this hospital in the last 3 years. As more experience is gained in the operative procedure, it is reasonable to anticipate further decreases in mortality.

The problems of thoracic aneurysms are more difficult than those in the lower aorta. The incidence of syphilitic lesions is distinctly higher, the general prognosis appears worse, and the operative treatment more difficult because temporary occlusion of the aorta in this region cannot be tolerated so well as below the level of the renal arteries. Neither the viscera nor central nervous system can withstand long periods of anoxia, whereas the extremities can. Various methods are being used to solve this problem, such as hypothermia and the use of vascular shunts. At present, the danger attendant on operating upon a thoracic aneurysm is considerably greater than upon an abdominal aneurysm, provided the latter lies below the renal arteries. Removal of the upper abdominal aorta has been accomplished,²⁴ but remains a hazardous undertaking. Total removal of the aortic arch has also been carried out,²⁵ but is even more hazardous.

According to Kampmeier,¹⁸ in patients with saccular thoracic aneurysms, "with few exceptions the duration of life after onset of symptoms is to be measured in months." The "average patient" with an aneurysm of the ascending aorta died in 8.0 months after the onset of

symptoms, in 6.4 months when the lesion arose from the transverse portion of the arch, and in 6.3 months if the lesion was in the descending aorta. Therefore, a considerable risk would seem well justified in an attempt to remove such a lethal condition; more and more successful cases of removal of thoracic aneurysms are being reported. Successes are particularly frequent with lesions that are distal to the left subclavian artery. Bahnson¹⁰ pointed out that syphilitic aneurysms in the chest are apt to be saccular and thus suitable for resection by clamping across their base without occluding the aorta. Aneurysms just distal to an area of coarctation of the aorta seem particularly favorable for resection because of the rich collateral circulation. The pathogenesis of such lesions is discussed by Holman.²³ This collateral circulation permits more prolonged obstruction of the aorta. With newer methods and more experience one can also anticipate improved results with excision of thoracic aortic aneurysms as a group.

Dissecting and ruptured aneurysms make up a definite proportion of aortic aneurysms that have not previously been diagnosed. Previously these lesions were nearly uniformly fatal.²⁶ The outlook today remains grave, but a significant proportion of these patients may be salvaged.^{22, 27-29} Although the terms "dissection" and "rupture" have been used interchangeably by some authors, the term "dissecting aneurysm" should be used only for those lesions in which the dissection involves the aortic wall, separating the intima and adventitia usually in the plane of the media. Such lesions ordinarily start in the arch of the aorta and then progress peripherally.³⁰⁻³² Infrequently they are self-limiting and may break back into the lumen of the vessel producing the so-called "double aorta."³³ Usually, however, the result is death within 2 weeks. After rather extensive work on this condition Gore³⁴ believed degeneration of the media to be the primary defect. In younger patients, even in the twenties, the elastic tissue is primarily involved in the degenerative process, whereas in older patients the smooth muscle seems to be at fault. In the intermediate age groups defects were found in both muscular and elastic tissues.

Hemorrhage into the media apparently initiates the process, and not necessarily a tear in the intima, which may remain intact. Syphilitic aneurysms are seldom reported to dissect, presumably because of the scarring in their media. Of the 85 fatal cases of dissecting aneurysms reported by Gore and Seiwart,³⁵ 19 were under the age of 30. Hypertension is common.³⁶ Recently DeBakey's group²⁷ described a successful method of dealing with these lesions. No one in our series was treated by this method, and all died; 1 patient has since been treated successfully by this method.

Rupture of an aneurysm is the term used for the condition in which blood has broken out of the wall of the vessel into the surrounding tissue. Very rarely these, too, may be self-limiting,¹⁴ but they ordinarily result in death within a few days or hours. When this situation exists, operation again offers the only real chance of survival. Such patients are often in severe shock when first seen, and the risk of operation is correspondingly high. If there is a chance of salvage, operation should be undertaken. In abdominal aneurysms, the blood usually dissects out in the retroperitoneal space and then into the peritoneal cavity, but rupture into the bowel may occur with hematemesis or melena as the first sign.³⁷ The retroperitoneal duodenum is the portion of gut most often involved, but ruptures into the stomach and other parts of the small bowel have been recorded.³⁸ Only 2 patients in this series survived under these circumstances, but others have reported better results.^{28, 29} If one can gain control of the aorta below the renal arteries before serious renal or other damage has occurred, there is a reasonable chance of saving the patient's life.

Although it is still too early to know how well arterial homografts or prostheses will stand the test of time, it has been demonstrated that the elastic tissue in human grafts remains for at least a year³⁹ by which time fibrous tissue has largely replaced the graft. Such grafts have now been used for 8 years⁴⁰ and it is clearly apparent that they may greatly prolong the lives of patients who have aneurysmal aortas.

SUMMARY

A group of 101 patients having aortic aneurysm is presented. Sixty-five of these lesions involved the abdominal aorta, and 36 the thoracic aorta. Operative and nonoperative groups are compared.

The incidence of abdominal aneurysms is increasing. If untreated, approximately one half of the patients with aortic aneurysms died within a year, and, of these, approximately one-half died of rupture of their lesion. Rupture or dissection of the aneurysms often occurred without premonitory symptoms. Excision of aortic aneurysms with restitution of blood flow by grafting, if needed, has improved the prognosis, and presumably will become less hazardous as more experience is gained in the procedure.

ACKNOWLEDGMENT

We would like to acknowledge the assistance of Dr. S. I. Askovitz and Mr. C. George in arranging the tabular data.

SUMMARIO IN INTERLINGUA

Es presentate un gruppo de 101 patientes con aneurysma aortic. In 65 del casos, le lesiones concerneva le aorta abdominal; in 36, le aorta thoracic. Es presentate un comparation del gruppo de casos operate con le gruppo del casos non-operate.

Le incidentia del aneurysmas abdominal se trova in stato de crescentia. In le gruppo del casos non-tractate, circa un medietate del patientes con aneurysma aortic moriva intra un anno, e in circa un medietate del mortes, le causa letal esseva ruptura del lesion. Ruptura o dissection del aneurysma occurreva frequentemente sin symptomatos premonitori. Le excision de aneurysmas aortic con restitution del fluxu sanguinee per medio de graffos in casos de necessitate ha meliorate le prognose e devenira sin dubita minus riscose in proportion al crescente experientia in le manipulation technic.

ADDENDUM

During the year 1956, 58 additional patients with aortic aneurysms were seen. Thirty-three had an abdominal aneurysm, 2 had abdominal and thoracic aneurysms, and 23 had thoracic aneurysms. Among

the latter group 7 patients had dissecting aneurysms and 3 had ruptured aneurysms. Among the abdominal aneurysms 7 were ruptured preoperatively.

In 11 patients with thoracic aneurysms an operation was performed. Of 3 patients with dissecting aneurysms who had a surgical procedure, 1 died of rupture of the aorta into the pericardium and 2 are living. Five patients had thoracic aneurysms successfully resected and 3 died during operation.

In the 27 patients with abdominal aneurysm, 5 had emergency procedures for ruptured aneurysms and these patients died; 5 patients were explored and their lesions were judged to be unsuitable for resection, 1 of these died from rupture of the lesion 2 weeks later; and 17 aneurysms were excised electively; 2 of these patients died, one because of renal failure and the other because of rupture of the graft.

This additional experience strengthens our belief that excision of aortic aneurysms is the treatment of choice.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Ewart's Sign. This was described by William Ewart (1848-1929), Physician to St. George's Hospital, in an article "Practical Aids in the Diagnosis of Pericardial Effusion, in Connection with the Question as to Surgical Treatment" which appeared in the *British Medical Journal* 1896 pp. 717-721 (March 21), 1896.

"Whenever fluid is effused into the pericardium the normal resonance is modified at the left posterior base in a most definite way. A patch of marked dullness . . . is found at the left inner base, extending from the spine for varying distances outwards, usually not quite so far as the scapular (angle) line, and ceasing abruptly with a vertical outer boundary. Above, its extension is also variable, according to the size of the effusion; commonly it does not extend higher than the level of the ninth or tenth rib, and here again its horizontal boundary is abrupt. Its shape then is that of a square, and it is quite unlike that of any dullness arising from pleuritic effusion. . . .

"Immediately below or slightly to the left of the tip of the left scapula a patch about 2 inches in diameter presents well-marked tubular breathing and aegophony. . . . This sign, although not so important as that of the patch of dullness, is very commonly, if not always, present in cases of considerable effusion, and gives valuable confirmation to other signs. It has been described by other observers. . . . It also occurs in pleural effusions."

Pulmonary Function in Left Ventricular Failure, Including Cardiac Asthma

By RICHARD S. COSBY, M.D., ELLERY C. STOWELL, JR., Ph.D., W. RAY HARTWIG, B.S., AND M. MAYO, A.B.

Unusually comprehensive studies of pulmonary function in hypertensive patients during left ventricular failure and cardiac asthma are presented. These findings are compared to those in mitral stenosis with congestive failure and in pulmonary emphysema with right heart failure. All patients were severely dyspneic and bedridden.

ALTHOUGH Harrison¹ and others have presented detailed studies of blood gases in left heart failure and cardiac asthma, and a number of papers on the experimental production of cardiac asthma and pulmonary edema are available,² there are no complete studies of the markedly abnormal respiratory patterns in this state. McCann³ in a recent review has referred to the elevation of arterial $p\text{CO}_2$ in the later stage of cardiac decompensation as "replacing the initial hypocapnia." Rodbard⁴ has emphasized the importance of bronchospasm in cardiac asthma. Our study will attempt to describe the respiratory pattern of left-sided heart failure in an effort to define the physiologic characteristics of such a state. Particular attention will be paid to the respiratory defects found in those patients with cardiac asthma. Studies of the respiratory patterns in mitral stenosis and in emphysema will be used for comparison and contrast.

MATERIAL AND METHODS*

Eight patients with hypertensive heart disease in congestive failure (group I), 14 patients with rheumatic heart disease, mitral stenosis, and congestive failure (group II), and 16 patients with emphysema and right heart failure (group III) were subjected to an evaluation of their pulmonary function. The

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* See Appendix for definitions of terms.

patients were selected specifically for their severe degree of dyspnea, irrespective of the presence or absence of wheezy respiration. All were bedridden at the time of examination. The usual lung volume studies were obtained, and analyses of distribution and diffusion were performed according to the techniques of Riley and co-workers.⁵ In addition, arterial oxygen saturations following positive pressure breathing, exercise, and 100 per cent oxygen were obtained in some of the patients. The expiratory flow pattern was analyzed by recording a pneumotachogram simultaneously with expiratory $p\text{O}_2$ and CO_2 curves, with both an infrared analyzer and a Beckman mass spectrometer. The mass spectrometer furnished information on alveolar oxygen, alveolar carbon dioxide, and pulmonary clearance. The linearity of response with gas concentration, the rapid inherent response time of the instrument, and its ability to monitor all respiratory gases consecutively rendered it invaluable.

RESULTS

The results of the ventilatory pulmonary function studies in all 3 groups are summarized in table 1. Because of the non-normal distribution of the data the measurements are summarized as medians in each category and non-parametric tests of statistical significance, in the analysis of variance and the 95 per cent confidence limits, were utilized.⁶ In table 1, patients in group I (hypertensive heart disease with congestive heart failure) show a marked reduction in vital capacity, maximum breathing capacity, air velocity index, and breathing reserve expressed as a per cent of maximum breathing capacity. In these 4 categories the hypertensive patients are significantly different from the patients with rheumatic heart disease. The ventilatory abnormalities in the hypertensive group are obstructive in nature.

In comparison with the cases in group I,

TABLE 1.—*Ventilatory Measurements*

	Hypertensive (8)		Rheumatic (14)		Pulmonary (16)	
	Median	95% Confidence limits	Median	95% Confidence limits	Median	95% Confidence limits
Vital capacity (% normal)§.....	44.7†	23.4-72.6	73.5†	54.7-79.5	44.5	30.7-60.6
Maximum breathing capacity (% normal)....	40.7*	13.6-65.7	58.8*	39.8-82.1	33.5*	22.1-39.2
Air velocity index.....	.666†	.305-1.55	.965†	.733-1.18	.658	.490-.869
Tidal volume ml.....	434	227-854	536	459-784	448	239-524
Ventilation (L./min./M. ²).....	4.46	3.33-6.34	5.00	4.09-6.05	5.01	3.69-6.46
Physiologic dead space as % tidal volume....	51.0	40.3-65.5	40.2	36.7-52.4	58.0	47.5-67.1
Alveolar ventilation (L./min./M. ²).....	2.40	1.64-3.22	3.64	2.52-4.09	2.24	1.66-2.98
Timed vital capacity in 3 seconds as % vital capacity.....	93.7	85.0-100	93.0	79.3-96.3	88.5	62.6-98.4
Breathing reserve as % Maximum breathing capacity.....	70.0†	36.4-88.6	85.0†	81.7-86.3	60.2†	47.6-73.5
Ventilation factor (%).....	45.5†	19.1-77.0	59.3†	43.7-79.9	40.9	29-58

* Differences between groups significant at the 5 per cent level.

† Differences between groups significant at the 1 per cent level.

‡ Significant at the 5 per cent level—hypertensive vs. rheumatic.

§ All ventilatory measurements expressed at body temperature, saturated ambient pressure.

patients in group II (rheumatic heart disease and mitral stenosis with congestive heart failure) have only a moderate ventilatory impairment; moreover, they show none of the bronchospastic features present in the hypertensive patient. This is more clearly brought out by the significantly higher ventilation factor in the patients with rheumatic heart disease. The ventilation factor of Motley⁷ averages 3 measurements: maximum breathing capacity, timed vital capacity, and residual air, expressed as a per cent of the predicted value in each case.

As expected, the patients in group III (emphysema with right heart failure) show marked differences from the group with mitral stenosis and congestive failure. The characteristic ventilatory defects in emphysema are clearly depicted in table 1—diminished vital capacity and maximum breathing capacity, low air velocity index, diminished ventilation factor, and a markedly low ratio of breathing reserve to maximum breathing capacity. The similarity of these data to comparable measurements in hypertensive heart disease with congestive failure is striking and again emphasizes the obstructive nature of respiration in both states. To be sure, these measurements are considerably more abnormal in emphysema, showing the greater obstructive element, as

exemplified by the comparison of the breathing reserve to maximum breathing capacity in both groups.

Blood gas studies in the 3 groups are summarized in table 2. Patients in group I show a significantly low arterial pO_2 and a significantly high arterial pCO_2 . Note that the high arterial pCO_2 leads to a low calculated alveolar pO_2 , a factor that appears to be responsible for the normal aeration gradient found in this group. The arterial oxygen saturation is somewhat below the normal, the transfer gradient is double the normal value, the per cent venous admixture is increased, and the oxygen diffusing capacity is somewhat reduced. There is a slight increase in arterial oxygen saturation on exercise and a slight decrease in the change in "true oxygen" after exercise.

In patients in group II the median value of arterial pO_2 is practically normal and the value of arterial pCO_2 is below normal. The aeration gradient is somewhat smaller than in group I, probably because of the lower arterial pCO_2 . The transfer gradient in group II is again double the normal value; the per cent venous admixture is within the normal range, although an occasional patient did show marked evidence of shunting. The oxygen diffusing capacity is lower than in group I, primarily due to impaired diffusion in patients with high pul-

TABLE 2.—Blood Gases

	Hypertensive (8)		Rheumatic (14)		Pulmonary (16)	
	Median	95% Confidence Limits	Median	95% Confidence Limits	Median	95% Confidence Limits
Arterial pO_2 mm. Hg.....	84.6*	47.9–100.1	94.1*	60.0–104.7	59.0*	45.1–68.3
Arterial pCO_2 mm. Hg.....	44.6*	35.5–47.7	36.0*	29.0–38.0	49.9*	43.4–54.4
% arterial O_2 saturation.....	93.8†	82.5–98.1	96.8	87.9–98.0	83.1‡	73.2–91.0
% change in above after exercise.....	+0.2	–0.3–+3.5	+2.3§	–2.7–+9.5	–4.6§	–7.57–0.3
No. reaching 100% after 100% O_2	All	—	5 of 7	—	6 of 9	—
Aeration gradient (mm. Hg).....	48.0†	39.3–56.8	39.0†	33.2–44.7	51.5†	45.3–77.3
Transfer gradient (mm. Hg).....	19.0†	6.6–51.7	20.0	7.0–58.4	34.0†	29.0–44.0
% venous admixture.....	11.5	3.0–20.0	5.0	1.0–27.0	35.0	22.0–45.0
O_2 diffusing capacity ml. O_2 /min./mm. Hg.....	12.3	8.1–16.5	8.0	7.0–11.7	8.3	6.1–15.0
True O_2 change after exercise.....	–0.2	–0.4–+0.8	–0.5§	–0.8–+1.0	+0.4§	–0.4–+0.9
pH.....	7.41	7.30–7.45	7.42	7.32–7.45	7.40	7.32–7.42
Pulmonary artery pressure (mm. Hg).....	—	—	44.0	35.0–58.0	46.0	13.0–91.0

* Differences between groups significant at the 5% level.

† Differences between groups significant at the 1% level.

‡ Significant at 5% level—pulmonary vs. hypertensive.

§ Significant at 5% level—pulmonary vs. rheumatic.

|| No. in groups too small for statistical analysis.

TABLE 3.—Ventilation and Blood Gas Studies in Eight Cases of Hypertensive Heart Failure

Vital capacity* % normal.....	20.0	24.9	38.0	40.4	63.0	49.0	60.4	92.0
Maximum breathing capacity % normal.....	10.9	3.1	15.0	31.4	50.1	70.0	63.3	50.0
Timed vital capacity as a % of vital capacity.....	95.5	86.0	90.0	92.3	100.0	100.0	95.0	83.0
Air velocity index.....	0.545	0.123	0.395	0.777	0.790	1.43	0.954	0.555
Ventilation factor (%).....	13.0	22.0	22.0	32.0	59.0	59.5	59.5	71.0
Breathing reserve as a % of Maximum breathing capacity.....	44.0	71.0	21.0	62.0	78.0	89.9	85.0	88.0
Physiologic dead space as a % tidal volume.....	52.3	40.0	51.0	71.4	52.0	48.0	—	40.9
Alveolar ventilation L./min./M. ²	1.40	3.45	2.32	2.16	2.71	2.59	—	2.40
Arterial pO_2 (mm. Hg).....	86.0	80.0	84.6	38.00	70.00	106.0	—	87.00
Arterial pCO_2 (mm. Hg).....	47.0	42.0	44.5	48.0	45.0	34.2	—	38.5
% arterial oxygen saturation.....	97.3	94.0	90.0	75.5†	93.6	98.9	97.8	93.6
Aeration gradient (mm. Hg).....	59.0	48.0	49.0	48.0	52.0	39.0	—	40.0
Transfer gradient (mm. Hg).....	15.0	22.0	17.0	65.0	28.0	5.0	—	19.0
Wheezing.....	+	+	+	+	+	0	0	0

* All ventilatory measurements expressed at body temperature, saturated, ambient pressure.

† Patient in pulmonary edema.

monary artery pressure. A larger increase in arterial oxygen saturation after exercise and decrease in true oxygen after exercise are present in this group.

In patients in group III the marked decrease in arterial pO_2 and increase in arterial pCO_2 are evident. The aeration gradient tends to be slightly larger than in group I. The transfer gradient is markedly larger than that found in

the other 2 groups, a factor undoubtedly related to the marked increase in the per cent venous admixture. The oxygen diffusing capacity is low, about equal to that found in group II. Striking differences are found in measurements taken after exercise. In group III, there is a marked fall in arterial oxygen saturation, and the true oxygen rises.

Table 3 shows the respiratory data in indi-

vidual patients in group I. The first 5 patients show severe bronchospastic respiration; these are considered to have cardiac asthma. They show a decrease in vital capacity, and a still greater decrease in maximum breathing capacity and breathing reserve. The other 3 patients had been admitted to the hospital in congestive heart failure, but did not present wheezy respiration at the time of examination. The ventilatory measurements are, on the whole, less abnormal in these 3 cases.

In their blood gas studies, the first 5 patients show a definite increase in arterial $p\text{CO}_2$; minimal arterial oxygen desaturation is present in 3 of the 5 cases, and 1 of these, in pulmonary edema, has an arterial saturation well below 90 per cent. It appears that the first 5 patients have true respiratory insufficiency in the same sense, but not in the same degree as do our patients with severe emphysema. Although the actual resting ventilation is increased above the normal range, a marked increase in the ratio of physiologic dead space to tidal volume is present, and thus the alveolar ventilation is inadequate. It is remarkable that such patients are able to maintain nearly normal arterial oxygen saturation with such diminished lung volumes, bronchospastic respiration, and arterial CO_2 retention.

Figures 1, 2, and 3 are diagrams of simultaneous pneumotachograms and $p\text{CO}_2$ and $p\text{O}_2$ curves of typical patients in each group, taken during expiration. These alveolar CO_2 and O_2 curves were obtained by the Beckman mass spectrometer. They portray the breathing pattern characteristic in hypertensive cardiac asthma, mitral stenosis with congestive failure, and also emphysema with right heart failure. In the typical patient in group I (fig. 1) the pneumotachogram shows a prolonged obstructive-type expiration with a low tidal volume. The normal curves are shown in each case for comparison. The alveolar $p\text{CO}_2$ level is somewhat above the normal level and the alveolar $p\text{O}_2$ level is reduced.

In the typical patient in group II (fig. 2), the pneumotachogram shows an increased tidal volume and no obstruction to expiration. The alveolar $p\text{CO}_2$ level is below the normal level, but the alveolar $p\text{O}_2$ is normal.

In the typical patient in group III (fig. 3),

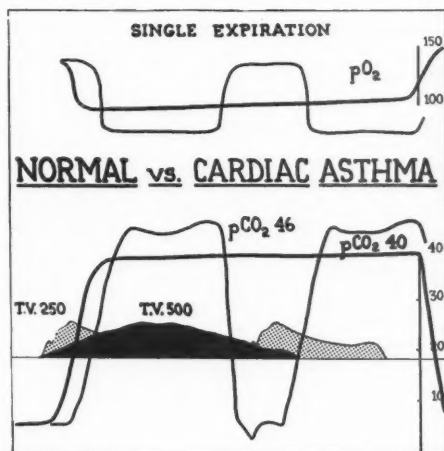


FIG. 1. Single breath analysis of alveolar $p\text{O}_2$, alveolar $p\text{CO}_2$, and tidal volume in hypertensive heart disease with congestive failure. Curves show decreased alveolar $p\text{O}_2$, increased alveolar $p\text{CO}_2$, diminished tidal volume (stippled), prolongation of expiration and tachypnea. Normal single breath alveolar $p\text{O}_2$, alveolar $p\text{CO}_2$ curves and tidal volume (black area) are presented for comparison.

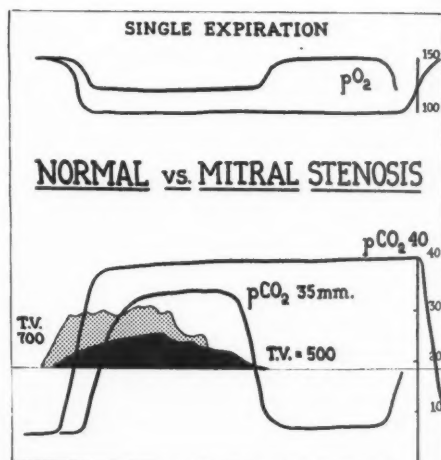


FIG. 2. Single breath analysis of alveolar $p\text{O}_2$, alveolar $p\text{CO}_2$ and tidal volume in rheumatic heart disease with mitral stenosis, and congestive heart failure. Curves show elevated alveolar $p\text{O}_2$, diminished alveolar $p\text{CO}_2$, large tidal volume (stippled) and no evidence of obstruction to expiration. Mild tachypnea was present. Normal single breath alveolar $p\text{O}_2$ and alveolar $p\text{CO}_2$ curves and tidal volume (black area) are presented for comparison.

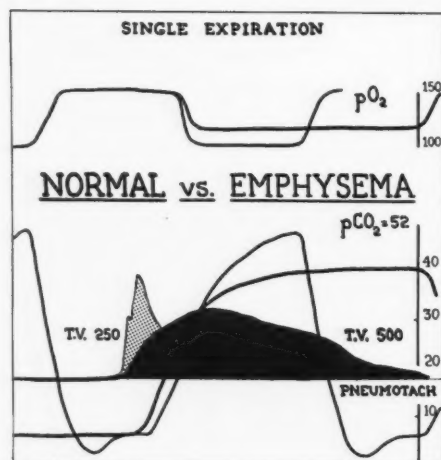


FIG. 3. Single breath analysis of alveolar pO_2 , alveolar pCO_2 and tidal volume in emphysema with right heart failure. Curves show diminished alveolar pO_2 and a marked increase in alveolar pCO_2 . A marked prolongation of expiration was present, characteristic of ventilatory insufficiency. Normal single breath alveolar pO_2 and pCO_2 curves and tidal volume (black area) are presented for comparison.

the resemblance to the pattern found in hypertensive heart disease with congestive heart failure is again evident. Here, even in the presence of a normal tidal volume, a pronounced obstruction to expiration is present. There is a markedly high alveolar pCO_2 level, and a low alveolar pO_2 .

DISCUSSION

The ventilatory measurements outlined in table 1 clearly demonstrate a marked difference between the hypertensive and the rheumatic patient with mitral stenosis in congestive heart failure. An obstructive-type ventilation is characteristic in the hypertensive in failure, and is most uncommon in the patient with mitral stenosis and heart failure.

Because of such differences, analyses of ventilatory and respiratory measurements in heart failure must take into consideration the underlying etiologic states. In the past, many authors studied lung volumes in heart disease as a whole. Richards and associates,⁸ for example, measured the lung volumes of patients with congestive heart failure, regardless of etiology. These authors stated that as heart

failure progressed, the complementary air diminished markedly, the reserve air became smaller than normal, with a marked decrease in vital capacity, and in extreme failure, the functional residual air was also smaller than the normal. Evidence was presented that increased heart size was an important factor in the production of these changes. No differentiation was made between hypertensive, coronary, or rheumatic heart failure.

The studies presented in table 1 emphasize the dissimilarities present in the 2 cardiac groups, particularly the markedly bronchospastic respiration characteristic of the hypertensive patient, and the lower vital capacity, breathing reserve and maximum breathing capacity found in group I.

The specific entity "cardiac asthma" was studied by Harrison,¹ who emphasized the marked decrease in vital capacity and concomitant increase in ventilation present in this state. Heyer⁹ studied 11 patients with cardiac asthma; 3 had cardiac asthma due to syphilitic aortic insufficiency, 4 had hypertensive heart disease, 2 had arteriosclerotic heart disease, and 2 had rheumatic heart disease with mitral stenosis. The spiograms in these patients were identical to those taken on patients with bronchial asthma. Prolongation of expiration was present in both conditions. The expiratory-inspiratory ratio (in seconds) was 1.61 in the normal; in cardiac asthma it was 2.67, and in bronchial asthma it was 2.14. Patients who did not show prolonged wheezing on physical examination might still have a prolongation of expiration well above the normal range. Patients with cardiac asthma improved after receiving aminophylline, with a definite increase in vital capacity.

Quite similar findings were reported by Plotz,¹⁰ who studied 9 patients; 5 had cardiac asthma due to hypertensive heart disease, 3 had cardiac asthma due to coronary heart disease, and only 1 had cardiac asthma due to rheumatic heart disease. These 9 patients were given epinephrine. The average vital capacity before epinephrine was 2.15 l., with an average increase of 425 ml. following epinephrine. Patients with basal rales but without prolonged expiration were not relieved by epinephrine.

He concluded that epinephrine relieved the bronchial spasm of cardiac asthma with an increase in vital capacity.

The data in table 3 showing the ventilatory data of individual patients with hypertensive heart disease with congestive heart failure present 5 patients who compare with those described by Harrison,¹ Heyer,⁹ and Plotz.¹⁰ The bronchospastic pattern described by Heyer⁹ and Plotz¹⁰ was essentially that of hypertensive heart disease and cardiac asthma, since only 3 of the combined 20 patients in the 2 series had rheumatic disease with mitral stenosis and cardiac asthma. The rarity of cardiac asthma in the presence of mitral stenosis is well known; none of the patients in our group II showed bronchospastic respiration or clinical wheezing.

Much attention has been given recently by Frank's group,¹¹ Richards,¹² and Cosby and associates¹³ to the ventilatory problems in mitral stenosis, with and without congestive heart failure. It was shown by Cosby and co-workers¹³ that the degree of dyspnea was more closely correlated with the height of the pulmonary artery pressure and with vital capacity than with maximum breathing capacity. The vital capacity was reduced but not to levels as low as those seen in hypertensive heart disease with failure. Little evidence of bronchospasm was present.

Frank and co-workers¹¹ stressed the increasing minute ventilation in this condition and pointed out that effective alveolar ventilation was maintained throughout all stages of disability. These authors re-emphasized the absence of obstructive defect. Richards¹² emphasized the discrepancy between the very moderate degree of ventilatory impairment and the marked degree of exertional dyspnea.

The relation between gas exchange and ventilation has been considered an important measurement of the degree of disability and has been employed to evaluate the cardiac element in dyspnea. McMichael,¹⁴ for example, noted a poor correlation between vital capacity and cardiac output but an excellent inverse correlation between the ventilatory equivalent for carbon dioxide and cardiac output. This was particularly useful in measuring sequential

changes in the same patient. He considered the ventilatory equivalent for carbon dioxide more critical than that for oxygen, since it was less dependent upon the respiratory quotient. Frank and co-workers¹¹ and Lindgren¹⁵ found an increased ventilatory equivalent for oxygen in mitral stenosis, but there was no relationship between the ventilatory equivalent and the degree of disability.

In the 3 groups studied in this laboratory, the only significant measurement related to gas exchange on exercise was the change in "true" oxygen on exercise. Patients with emphysema were able to increase the amount of oxygen extracted from inspired air slightly, although the increase was not a normal one. On the other hand, patients in the rheumatic group showed a significant decrease in "true" oxygen on exercise. Measurements of ventilatory equivalents were not conclusive, although all were somewhat elevated at rest. Because of the unstable cardiorespiratory state of most of these patients it would seem likely that a derived measurement so dependent upon ventilation would have greater variability than the per cent change in "true" oxygen on exercise.

Several authors have studied blood gas exchange in heart disease. Varnauskas¹⁶ has recently reported on 49 hypertensive patients in varying degrees of congestive failure, who showed a mean arterial desaturation of 3 per cent below the normal. Harrison¹ reported on 5 patients with similar disability; 2 fell below 90 per cent. The most extensive study of the alveolar-arterial gradient in cardiac subjects has been presented by Storstein.¹⁷ He studied 4 patients with hypertensive heart disease, 15 patients with rheumatic heart disease, and 8 patients with pulmonary disease and emphysema. Median arterial oxygen saturations were as follows: 93.8 per cent (91.9 to 94 per cent) in the hypertensive group; 93.2 per cent (80.0 to 98.7 per cent) in the rheumatic group; and 83.0 per cent (76.9 to 90.7 per cent) in the pulmonary group. Median alveolar-arterial gradients were as follows: 23.4 mm. (18.5 to 37.7 mm.) in the hypertensive group; 21.5 mm. (6 to 33 mm.) in the rheumatic group; and 47.5 mm. (31.3 to 55.0 mm.) in the pulmonary group. There is close agreement between Storstein's¹⁷ data and

the data shown in table 2 relative to arterial oxygen saturation and the transfer gradient. The patients in our group III did not show quite such striking increases in the transfer gradient as did Storstein's¹⁷ comparable group. However, the agreement in the 2 series as a whole is noteworthy, especially on consideration of the fact that Storstein¹⁷ made no mention of the degree of disability in any of his patients; moreover, the arterial pO_2 in Storstein's¹⁷ series was calculated indirectly from the oxygen dissociation curve, while in our groups the arterial pO_2 was measured directly by Riley's technic.⁵

With respect to abnormalities of distribution and diffusion, there are no specific studies available on patients in congestive heart failure. The data of Fowler and associates¹⁸ and Carroll and associates¹⁹ refer to patients with mitral stenosis, with or without heart failure. Of the 13 patients studied by Fowler's group¹⁸ only 1 was described as being in congestive failure at the time of examination. These authors specifically chose patients with increasing levels of pulmonary artery pressure and noted that in the 5 showing a decrease in oxygen diffusing capacity, 4 had markedly increased pulmonary artery pressure. Of the other 8 patients with lower pulmonary artery pressure, 5 showed an increase in per cent venous admixture and 6 showed an increase in the ratio of dead space to tidal volume.

The data in table 2 confirms those of Fowler and associates¹⁸ and Carroll and associates,¹⁹ revealing a marked reduction in oxygen diffusing capacity in the presence of elevated pulmonary artery pressure. A significant increase in per cent venous admixture was present in only 1 patient with rheumatic heart disease and 1 patient with hypertensive heart disease, both in pulmonary edema. The ratio of physiologic dead space to tidal volume was somewhat higher in the hypertensive than in the rheumatic group in our series.

Finally, the small group of patients with hypertensive heart disease and the severest degree of cardiac asthma deserves special mention. The presence of CO_2 retention in cardiac asthma has not been previously emphasized, although Peters and Barr²⁰ had

found increases of arterial pCO_2 up to 52 mm. in cardiac asthma. McCann³ believed that the initial hypocapnia in heart disease was replaced by elevation of the arterial pCO_2 as congestive failure became more severe. It seems most significant that those with the most pronounced degree of cardiac asthma had the lowest vital capacities and the highest arterial pCO_2 in the cardiac groups. This small group strongly resembled the patients with emphysema and right heart failure. Nevertheless their arterial oxygen saturation was minimally reduced, an effect that may have been due to the positive pressure effect of bronchospastic respiration.

SUMMARY

In hypertensive heart disease with congestive heart failure, a marked reduction is present in vital capacity, maximum breathing capacity, air velocity index, and breathing reserve expressed as a per cent of maximum breathing capacity. Although not all of the patients complained of the wheezing characteristic of cardiac asthma, the majority of the patients with hypertensive heart disease in failure have an obstructive type of ventilatory impairment. Minimal abnormalities of diffusion, moderate increases in the physiologic dead space and minimal increases in the per cent venous admixture are present. Only in an occasional patient with frank pulmonary edema is marked arterial desaturation present. When cardiac asthma is severe, the vital capacity and maximum breathing capacity are markedly reduced, and true respiratory insufficiency with CO_2 retention ensues.

In rheumatic heart disease, mitral stenosis and failure, at a comparable level of disability, only moderate ventilatory impairment exists. The vital capacity is the measurement that most clearly reflects the ventilatory disability and obstructive ventilatory features are extremely rare. Ventilation tends to be greater than in hypertensive heart disease and thus the aeration gradient is significantly lower. The arterial pCO_2 is significantly reduced below the normal range. Greater abnormalities of diffusion are present than in the hypertensive group, and there is also an increase in the ratio

of physiologic dead space to tidal volume. Significant arterial oxygen desaturation is rare.

Patients with pulmonary emphysema at a comparable level of disability follow the known established patterns of respiratory impairment. There is a marked increase in residual air, and the obstructive ventilatory insufficiency strongly resembles the pattern found in hypertensive heart disease. However, the transfer gradient and per cent venous admixture are both far greater than in hypertensive heart disease, the arterial $p\text{CO}_2$ is higher and arterial oxygen saturation is lower than in cardiac patients with congestive failure. Thus blood gas measurements rather than ventilatory measurements more adequately separate the cardiac and pulmonary groups.

CONCLUSIONS

The characteristic respiratory pattern in patients with hypertensive heart disease with congestive failure and with cardiac asthma is one of obstructive ventilatory insufficiency, low vital capacity and maximum breathing capacity, minimal arterial oxygen desaturation, and arterial $p\text{CO}_2$ retention. In contrast, patients with mitral stenosis and congestive failure show hyperventilation, only moderate ventilatory impairment with no obstructive features, and a low arterial $p\text{CO}_2$. Patients with pulmonary emphysema, at a comparable level of disability, show a higher residual air and a lower breathing reserve. There is a greater degree of arterial oxygen desaturation, a far higher transfer gradient, a larger increase in per cent venous admixture, and a higher arterial $p\text{CO}_2$ than in patients with heart disease and congestive failure.

ACKNOWLEDGMENT

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SUMMARY IN INTERLINGUA

In morbo cardiac hypertensive con congestive disfallimento cardiac, un marcate reduction se manifesta in le capacitate vital, le capacitate respiratori maximal, le indice del

velocitate aeree, e le reserva respiratori exprimate in pro cento del capacitate respiratori maximal. Ben que non omne le patientes se plangeva del rhoncho characteristic de asthma cardiac, le majoritate del patientes con morbo cardiac hypertensive in disfallimento suffre de un typo obstructive de disturbance ventilatori. Es a notar minimal anormalitates de diffusion, moderate augmentos del spatio morte physiologic, e minimal augmentos in le percentage del admixtion venose. Marcate dissaturation arterial se trova solmente in rar patientes con franc edema pulmonar. Quando le asthma cardiac es sever, le capacitate vital e le capacitate respiratori maximal es marcatamente reduce, e ver insufficientia respiratori se disveloppa con retention de CO_2 .

In morbo cardiac rheumatic, stenosis mitral, e disfallimento, il existe a comparabile nivellos de invaliditate solmente moderate grados de disturbance ventilatori. Le capacitate vital es le mesura que reflecte le plus clarmente le incapacitate ventilatori, e obstructive tractos ventilatori es extremamente rar. Le ventilation tende a esser plus grande que in morbo cardiac hypertensive, e assi le gradiente de aeration es significativamente plus basse. Le $p\text{CO}_2$ es reduceite a grados significative-mente infra le limites normal. Plus grande anormalitates de diffusion es presente que in le gruppo hypertensive, e il se nota etiam un augmento in le proportion inter le spatio morte physiologic e le volumine del aere corrente. Grados significative de dissaturation arterial de oxygeno es rar.

Patientes con emphysema pulmonar a nivellos comparabile de incapacitate obedi le establite e cognoscite modello de disturbance respiratori. Il occorre un marcate augmento del aere residue, e le obstructive insufficientia ventilatori es multo simile a lo que es trovate in morbo cardiac hypertensive. Tamen, le gradiente de trasferimento e le pro cento del admixtion venose es ambe multo plus grande que in morbo cardiac hypertensive, le $p\text{CO}_2$ es plus alte e le saturation arterial de oxygeno es plus basse que in patientes con disfallimento congestive. Assi, mesurationes del gases del sanguine serve plus adequatemente

que mesuraciones ventilatori a separar le gruppo cardiac e le gruppo pulmonar.

Le sequente conclusiones es presentate: Le configuration characteristic del respiration in pacientes con morbo cardiac hypertensive associate con disfallimento congestive e con asthma cardiac es distinguite per obstructive insufficientia ventilatori, basse capacitate vital e maximal capacitate respiratori, minimal dissaturation arterial de oxygeno, e retention arterial de $p\text{CO}_2$. In contrasto con isto, pacientes con stenosis mitral e disfallimento congestive exhibi hyperventilation, solamente moderate grados de disturbance ventilatori con nulle characteristics obstructive, e un basse $p\text{CO}_2$ arterial. Patientes con emphysema pulmonar a comparabile nivellos de incapacitate monstra un plus grande volumine de aere residue e plus basse reservas respiratori. Il se nota in iste casos un plus alte grado de dissaturation arterial de oxygeno, un multo plus alte gradiente de transferimento, un plus grande augmento del procentage de admixtion venose, e un plus alte $p\text{CO}_2$ arterial que in pacientes con morbo cardiac e disfallimento congestive.

APPENDIX—DEFINITIONS

1. Vital capacity is the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration (ml.).

2. Inspiratory reserve volume (formerly complementary air) is the maximal amount of gas that can be inspired from the end-inspiratory position (ml.).

3. Expiratory reserve volume (formerly reserve or supplemental air) is the maximal volume of gas that can be expired from the end-expiratory level (ml.).

4. Residual volume is the volume of gas remaining in the lungs at the end of a maximal expiration, customarily expressed as a per cent of the total capacity (ml.).

5. Maximal breathing capacity is the maximal volume of gas that a subject can breath out per minute, usually measured over a 15-second interval (L./min.).

6. Air velocity index is the per cent predicted maximum breathing capacity divided by the per cent predicted vital capacity.

7. Tidal volume is the volume of gas inspired or expired during each respiratory cycle (ml.).

8. Ventilation is the volume of air expired per minute, expressed in liters per minute per square meter body surface.

9. Physiologic dead space is the volume of air in the trachea and bronchi (anatomic dead space) and

in addition air from alveoli where circulation is reduced or absent. It is calculated by the Bohr equation, expressing the relationship of arterial and expired $p\text{CO}_2$. It is customarily expressed as a per cent of tidal volume.

10. Alveolar ventilation is the total ventilation minus the dead space ventilation, expressed in liters per minute per square meter body surface.

11. Timed vital capacity is the volume of the total vital capacity expired in 3 seconds, expressed as a per cent of the vital capacity.

12. Breathing reserve as a per cent of maximum breathing capacity is the maximum breathing capacity minus resting ventilation divided by the maximum breathing capacity.

13. Ventilation factor is an average of (1) the 3-second timed vital capacity as a per cent of predicted vital capacity; (2) the maximum breathing capacity as a per cent of its predicted value; and (3) the normal residual air as a per cent of total lung volume divided by the observed residual air as a per cent total lung volume.

14. Aeration gradient is the $p\text{O}_2$ of inspired air minus the $p\text{O}_2$ of the alveolar air.

15. Transfer gradient is the $p\text{O}_2$ of alveolar air minus the $p\text{O}_2$ of arterial blood.

16. Venous admixture is the quantity of mixed venous blood reaching the peripheral arterial blood from right to left shunts such as bronchial and thebesian veins and abnormally from capillary blood in alveoli in which ventilation is reduced in relation to perfusion. It is expressed as a per cent of cardiac output.

17. Oxygen diffusing capacity is a measure of the permeability to oxygen of the alveolo-capillary membrane of the lung as a whole. The oxygen intake per minute divided by the calculated mean oxygen pressure gradient along the length of the capillary is the oxygen diffusing capacity, expressed as ml. oxygen per minute per mm. Hg.

18. True oxygen is the amount of oxygen extracted from inspired air, expressed in per cent per liter of expired air.

19. Ventilatory equivalent for carbon dioxide (or oxygen) is the minute volume of air in liters divided by each 100 ml. of oxygen consumed or carbon dioxide produced.

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I affirm likewise of the blood in the veins, that the blood does always, and every where, run out of the lesser into the greater, and hastens towards the heart from every part: whence I gather that whatsoever quantity which is continually sent in, the arteries do receive by the veins, that the same does return and does at last flow back thither from whence it is first driven, and that by this means the blood moves circularly, being driven in its flux and reflux by the heart, by whose force it is driven into all the fibres of the arteries, and that it does afterwards successively by a continual flux return through the veins, from all those parts which draw, and streyn it through; sense it self teaches us that this is true, and collections from things obvious to sense takes away all occasion of doubt.—WILLIAM HARVEY, *De Circulatione Sanguinis*, 1649.

Diagnostic and Prognostic Significance of Serum Transaminase Levels in Coronary Occlusive Disease

By A. A. KATTUS, M.D., R. WATANABE, M.D., AND C. SEMENSON, M.D.

With technical assistance of Joe Yamashita

Clinical and experimental studies of acute myocardial infarction suggest that serum glutamic oxalacetic transaminase (SGO-T) levels may have both diagnostic and prognostic significance. The authors report their experience in 255 patients hospitalized because of chest pain strongly suggestive of acute myocardial infarction. The results of serial determinations are compared with the clinical data and the electrocardiographic findings. The data indicate that abnormally high levels have both diagnostic and prognostic significance.

CLINICAL and experimental studies of acute myocardial infarction¹⁻⁷ have suggested that the serum glutamic oxalacetic transaminase (SGO-T) test devised by LaDue and his associates may have both diagnostic and prognostic significance. The present report contains data on 255 patients all of whom were hospitalized with chest pain strongly suggesting myocardial infarction in the differential diagnosis.

These data indicate that the test is of diagnostic value, particularly in patients in whom the diagnosis cannot be made with certainty from the electrocardiographic findings and other clinical features. A study of the fatal cases suggests that the test also has prognostic significance.

METHODS

The patients were all hospitalized either at the Wadsworth General Veterans Administration Hospital or at the UCLA Medical Center. All but 3 of the patients were men ranging in age from 37 to 85 years. Efforts were made to obtain serial SGO-T determinations, particularly during the first few days following the onset of pain, since the time-concentration curve of the SGO-T levels has been shown to be far more informative than single ran-

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Abstracted, *Circulation* **12**: 729, 1955.

dom samples.³ Cases with only 1 determination were excluded from the study unless that sample was markedly elevated and appeared to be significantly related in time to the onset of pain or to the death of the patient.

The SGO-T levels were determined by the method of Karmen⁸ with slight modifications as described earlier.³ Some batches of malic dehydrogenase required dilution of 1 to 10 in phosphate buffer rather than 1 to 25 as previously done.

In order to assess the diagnostic value of the test the cases were divided into those with proved myocardial infarction and those in whom the diagnosis of myocardial infarction could not be made with certainty.

The cases were considered to have proved infarction if the history was compatible with the diagnosis and the electrocardiograms showed pathologic Q waves and typical evolutionary ST and T-wave patterns of acute myocardial infarction; 111 cases fell into this group.

There were 144 cases in whom the diagnosis of myocardial infarction remained in question, either because the clinical manifestations were not clear or the electrocardiograms failed to show the typical pattern of acute myocardial infarction. In many instances the electrocardiographic patterns were obscured by pre-existing abnormalities. It is true that a number of the cases in this group did have clinical manifestations that merited strong suspicion of acute myocardial infarction, but in none of them could the diagnosis be made with certainty. Seven patients classified initially as probable myocardial infarctions were later shown to have infarcts at autopsy.

The idea of the study was to examine the reliability of the test in patients with known myocardial infarction and then to ascertain whether the test would enable us to pick the instances of infarction from the cases in which the diagnosis was uncertain. To determine the prognostic value of the SGO-T test the peak of the time-concentration curve was examined in the fatal cases.

RESULTS

*Evidence of Diagnostic Significance**Patients with Proved Myocardial Infarction.*

Al but 1 of 111 cases of proved myocardial infarction had elevated SGO-T. The distribution of SGO-T levels during the acute phase of the attacks is illustrated in figure 1. Normal values of SGO-T may be found during the first few hours after the onset of pain. The values rise rapidly to a peak that is usually reached between 24 and 48 hours after the onset. There is then a gradual fall over the succeeding 3 or 4 days to normal levels. The patient with no rise in SGO-T died only 3½ hours after the onset of pain. Thus, all cases of proved myocardial infarction showed an elevation of SGO-T, provided serial blood samples were taken during the first 4 days of the disease. The elevation may be missed if blood samples are taken too early or after the third or fourth day.

It is of interest that 7 of the 111 cases of proved myocardial infarction showed elevation of SGO-T before the electrocardiographic patterns became clearly diagnostic, which thus provided early evidence of myocardial necrosis.

Patients with Uncertain Diagnosis. Among 144 cases in which the diagnosis of myocardial

infarction could not be established with certainty, 63 had SGO-T elevations with peak levels of 44 to 800 units. These 63 cases have been classified as "probable myocardial infarction," since they all had elevations of SGO-T with time-concentration curves similar to those of cases with proved infarction. Eight of the probable cases died and 7 of them came to autopsy; all 7 showed recent myocardial infarction. Examples from the group of probable infarctions are presented in the section on illustrative cases.

The electrocardiographic features that obscured diagnosis in this group are listed in the first column of table 1 and the peak levels of SGO-T are illustrated in figure 2.

Among the uncertain cases were 10 patients who had slight elevations of SGO-T ranging from 40 to 43 units, hardly out of the normal range. Each of these, however, had a well-defined curve with a rise to the peak value and a subsequent fall to much lower levels. Because of our conviction that the sequence of SGO-T levels is more important than any single value, we have thought it likely that these patients did have small infarctions. We have listed them as "possible infarctions" in table 1 and plotted them as such in figure 2.

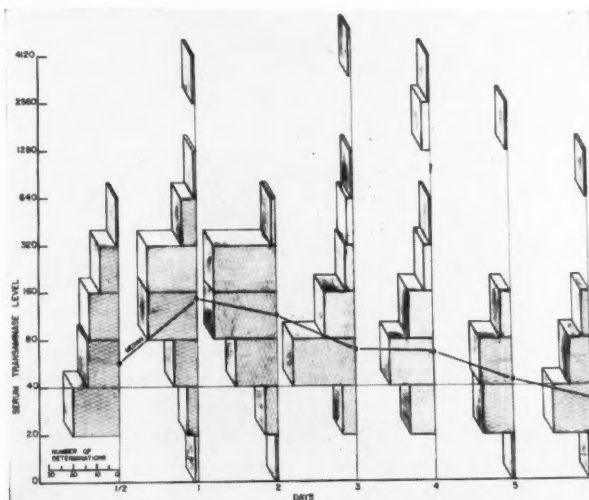


FIG. 1. Frequency distribution of SGO-T levels on each of 6 successive days following the clinical onset of the disease in 118 patients with proved myocardial infarction. The ordinate is logarithmic. All cases showed elevations above 40 units at some time during these 6 days.

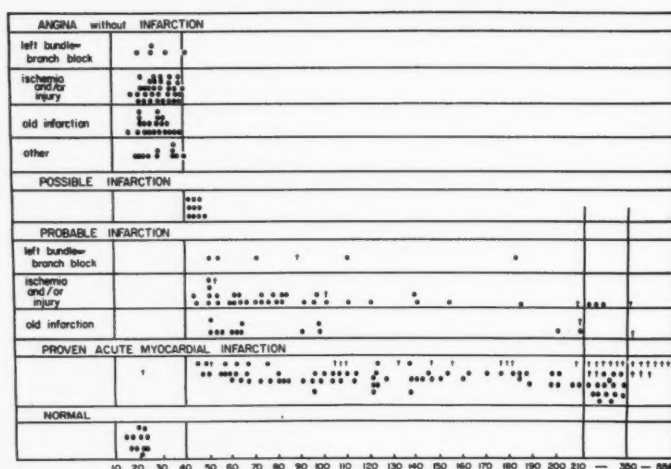


FIG. 2. Distribution of peak SGO-T levels in various clinical categories with subdivisions indicating electrocardiographic patterns. The category marked "other" includes cases of ventricular "strain," arrhythmias, flat T waves, cor pulmonale, dissecting aneurysm, and normal electrocardiogram. Seven of 8 fatal cases with uncertain diagnosis during life became proved cases at autopsy. (• Indicates survivals and † indicates deaths.)

TABLE 1.—Cases with Chest Pain of Uncertain Diagnosis

Electrocardiographic and clinical diagnosis	Number of cases with SGO-T elevations: "probable infarct"	Number of cases with slight SGO-T elevations: "possible infarct"	Number of cases with no SGO-T elevations: "angina without infarct"	Total
Injury or ischemia..	37	5	34	76
Previous MI†.....	15	3	21	39
LBBB*.....	6	1	5	12
Ventricular "strain"	3	1	3	7
Normal electrocardiogram.....			3	3
Arrhythmia.....			2	2
Flat T waves.....			1	1
Cor pulmonale.....			1	1
Dissecting aneurysm.....			1	1
No electrocardiogram taken.....	2			2
Total.....	63	10	71	144

* Left bundle-branch block

† Myocardial infarction

There were 71 patients who showed no rise of SGO-T in serial determinations. Several of these had levels as high as 40 units but on serial determinations these showed very little or no variation. It was concluded that these patients in all likelihood had anginal pain without

infarction. These cases are listed in the third column of table 1 and plotted in the top section of figure 2.

In the groups listed as "possible infarction" and "angina without infarction" there were no deaths, so that autopsy confirmation was not possible in any of these cases.

Extension of Known Myocardial Infarction. Among the patients with proved myocardial infarction, 14 had recurrences of chest pains accompanied by secondary rises of the SGO-T levels. In a number of these, additional electrocardiographic changes could not be discerned. In such cases SGO-T elevations provided the strongest evidence of extension of previously known acute myocardial infarction. Three of these cases are illustrated in the next section.

Illustrative Cases. Figure 3 depicts the course of a 60-year-old white man who had severe substernal crushing pain with sweating and dyspnea. The electrocardiograms showed only the slightest abnormalities consisting of some loss of voltage and flattening of the T waves. The leukocyte counts and the sedimentation rates did not help in the diagnosis, but the SGO-T curve gave strong evidence of the presence of infarction.

Figure 4 shows the course of a 60-year-old white diabetic man, who was admitted with severe chest pain and dyspnea. The electrocardiogram showed only slight ST sagging in V. SGO-T levels remained normal and it was concluded that the patient had anginal pain without infarction. He continued to have inter-

mittent substernal pains during the next several weeks. Subsequently there was a recurrence of severe chest pain accompanied by marked ST depressions in the electrocardiogram without Q waves. SGO-T rose sharply and the patient expired. At autopsy, there was extensive subendocardial myocardial infarction. In this

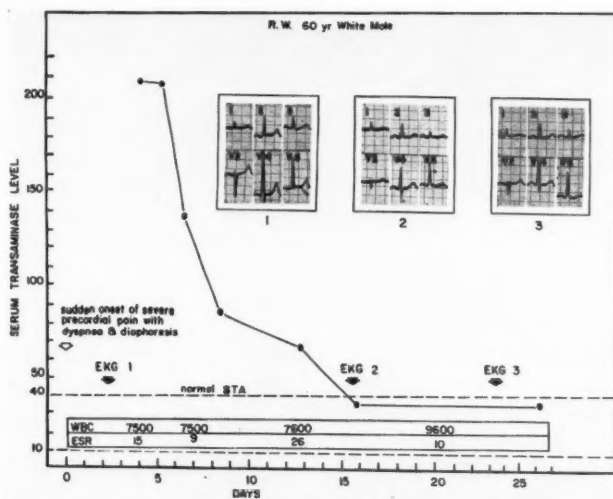


FIG. 3. Almost normal electrocardiogram. Probable infarction suggested by history and high SGO-T levels.

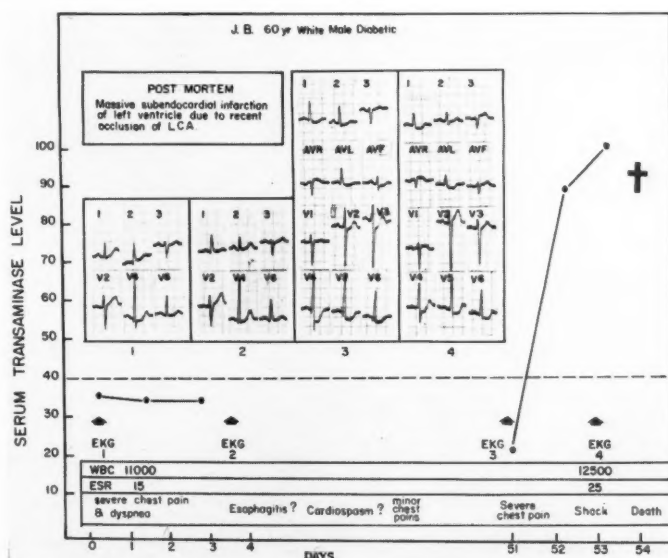


FIG. 4. Coronary insufficiency with normal SGO-T levels followed by subendocardial injury and high SGO-T. Infarction established at autopsy.

case the SGO-T test first aided in excluding the presence of myocardial infarction and later helped to confirm its presence.

Figure 5 illustrates the case of a 67-year-old white man who was admitted with substernal pain and fever. The electrocardiogram showed only slight ST depressions but the elevation and subsequent fall of SGO-T gave evidence of myocardial infarction. Two months later a recurrence of pain was accompanied by electrocardiographic changes indicative of posterior myocardial infarction. SGO-T elevations present at this time fell to normal. A subsequent attack of pain was not accompanied by definitive electrocardiographic changes, but the rise in SGO-T indicated extension of the infarction.

Figure 6 depicts the course of a 55-year-old white man with a history of an old myocardial infarction. The patient suffered 4 different episodes of chest pains during which the electrocardiogram continued to show a slightly varying pattern of myocardial injury and ischemia. Three of these episodes appeared to be true infarctions, since each was accompanied by elevations of SGO-T. The last episode was associated with no rise and presumably was a bout of coronary insufficiency.

Figure 7 shows the value of the low-level curve. This patient was a 58-year-old white man with chest pain and electrocardiographic evidence of posterior myocardial infarction. Although the peak SGO-T level of 44 units was only slightly higher than the normal range, the rise and fall of the level was strongly suggestive of myocardial infarction.

Figure 8 depicts the course of a 64-year-old white man who had clear-cut electrocardiographic evidence of acute posterior infarction accompanied by SGO-T elevation. Two further episodes of chest pains were not accompanied by further electrocardiographic changes but marked secondary and tertiary elevations of SGO-T gave strong evidence of the presence of extensions of the area of infarction. There was infarction of the entire posterior wall of the heart including septum and left and right ventricles at autopsy. Areas of fresh red hemorrhagic necrosis were clearly delineated from older areas of grey and yellow necrosis.

Evidence of Prognostic Significance

Experimental work in animals⁵⁻⁷ has indicated that the height of the peak level of SGO-T is roughly proportional to the size of myocardial infarcts. If this is also true in man, then

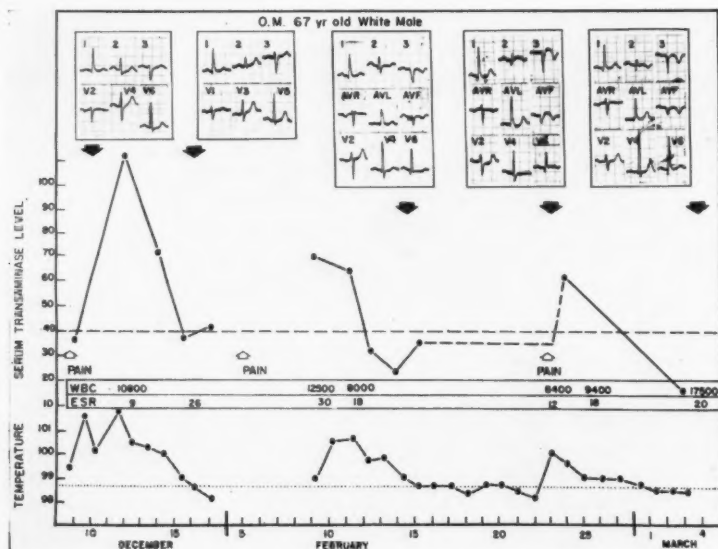


FIG. 5. Slight ST depressions only, but high SGO-T and fever indicate presence of infarction. A subsequent episode of unequivocal posterior infarction followed by lateral extension.

the SGO-T test should have important prognostic implications: the larger the infarct, the poorer should be the prognosis and the higher the mortality. One might expect, therefore, that the patients who died would have higher peak

levels of SGO-T than the survivors of myocardial infarction, and furthermore, that the larger infarctions would be associated with higher levels of SGO-T than the smaller infarcts.

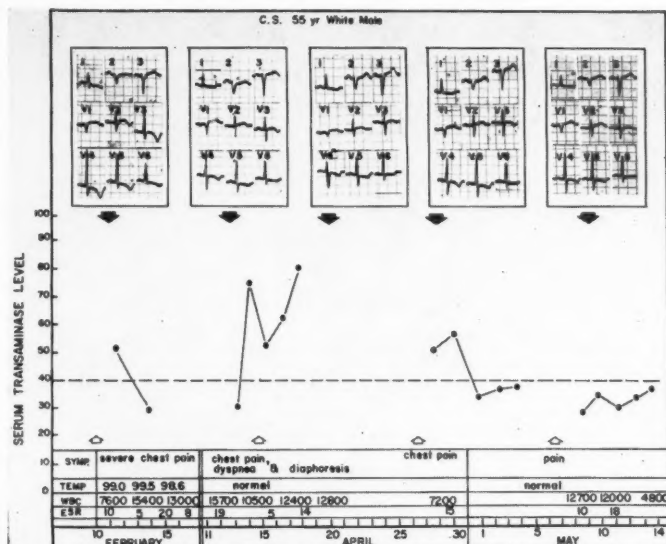


FIG. 6. Four episodes of chest pain with electrocardiograms showing only ischemia. During 3 of the episodes SGO-T is elevated, suggesting infarction. In the fourth SGO-T is normal, suggesting anginal pain without infarction.

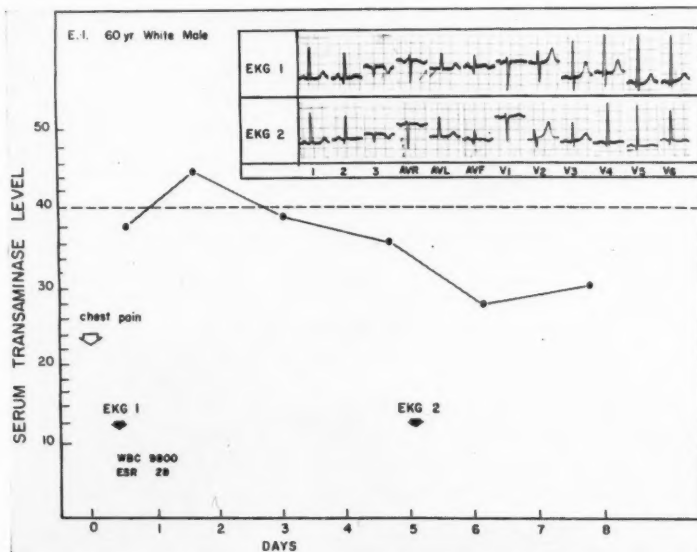


FIG. 7. Shows that low-level SGO-T elevations are significant. Electrocardiogram shows typical posterior myocardial infarction. SGO-T rises only to 44 units.

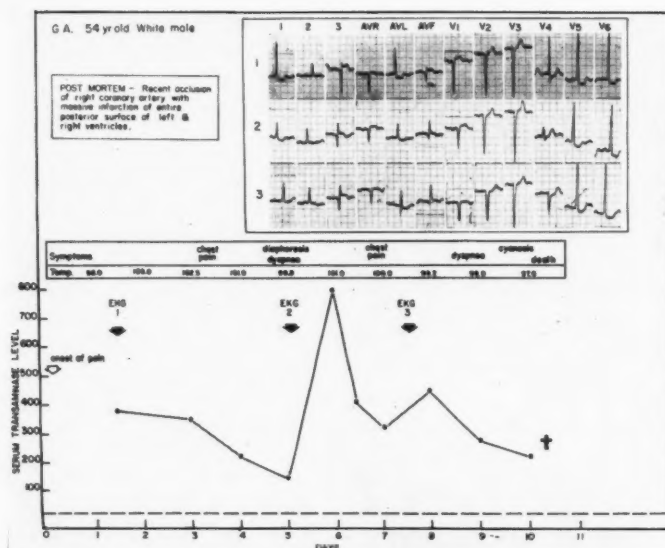


FIG. 8. Illustrates the value of SGO-T in discerning extension of proved infarction. Extensions indicated by secondary and tertiary rises of SGO-T although electrocardiograms do not change.

To find evidence bearing on this problem a study was made of the 37 fatal cases. All but 3 of these were autopsied. It was apparent that many of the fatal cases had peak SGO-T levels no higher than the survivors. Many were associated with complicating factors such as previous myocardial infarction, other diseases, or a failure to obtain blood samples at a time when peak values of SGO-T were to be expected.

For a valid evaluation of the significance of SGO-T in fatal cases it is necessary that death be clearly due to the acute infarction and that it occur after the peak of the SGO-T. It is also necessary that other complicating factors be absent that might make the patient succumb to myocardial damage which, in itself, might not be lethal. In our series only 11 of the 37 fatal cases fulfilled these conditions reasonably well.

Table 2 summarizes the data on the fatal cases. The 11 cases that fulfilled our conditions are listed separately. The 26 cases with complicating factors are summarized in 4 groups. One group of 7 cases contains patients who died of recent infarctions superimposed on well-established previous infarction. In this situa-

tion it might be presumed that a relatively small infarct would be sufficient to destroy the previously damaged heart. Another group contains the 6 patients who died of infarctions complicating other disease processes: 2 occurred following major surgery, 3 were associated with lobar pneumonia, and 1 complicated cirrhosis of the liver. In the third group are 7 fatal cases with insufficient SGO-T tests to define the peak level. The last group is composed of 6 patients who died a week or more following the primary SGO-T curve without further determinations.

The 11 separately listed cases, with one exception, did indeed have higher peak SGO-T levels than any of the survivors. The highest level found among survivors of proved or probable myocardial infarction was 336 units. There were only 5 survivors with peak levels over 300. The very high levels above 1000 units were all associated with profound shock in the preterminal state. The highest level of all, 5567 units, occurred in a patient in whom hypothermia at 85 F. had been induced in an effort to prolong his life. That shock does not always produce extremely high levels is indicated from the observation that patient F.S.

TABLE 2.—Fatal Cases Studied by SGO-T Test

Patient	Peak SGO-T	Clinical	Autopsy
H. I. 60 yr. W, M.	5567	Profound coronary shock-induced hypothermia to 84 F.	Extensive infarction of left ventricle
W. J. 61 yr. W, M.	2900	Entered moribund, single sample before death	Massive infarction left ventricle and septum, small infarcts left kidneys and adrenals
D. S. 63 yr. W, M.	1940	Profound shock, poor response to Levophed	Extensive posterior infarction
I. V. 57 yr. W, M.	820	Profound shock, recurrent infarction	Extensive posterolateral infarction
G. A. 54 yr. W, M.	800	No shock, two extensions	Massive infarction of posterior right and left ventricle and septum
F. S. 64 yr. W, M.	675	Shock and ventricular tachycardia	Extensive infarction of septum and posterolateral left ventricle
S. H. 46 yr. N, M.	580	No shock	Massive posterior and old anterior infarct
A. W. 33 yr. W, M.	560	Congestive failure, no shock	Extensive posterior infarction
C. G. 60 yr. W, M.	523	Congestive failure, no shock	Extensive infarction of posterolateral left ventricle and posterior right ventricle
R. M. 64 yr. W, M.	357	No shock	Extensive infarction left ventricle and septum
P. W. 56 yr. W, M.	156	No shock, sudden death on 4th day	3 x 4 cm. infarction of posterior left ventricle and septum
7 cases	50 to 210		Died of recent infarct complicating old one
6 cases	50 to 218		Died with infarct complicating other diseases
7 cases	23 to 293		Died with peak value not known
6 cases	146 to 242		Died a week or more after primary curve

had severe shock with a peak level of 675, while patient G.A. had no shock when his level was 800. One survivor went through a period of 11 hours of severe shock with a level of SGO-T that did not rise above 298.

These data give convincing evidence that high levels of SGO-T do indeed carry a poor prognosis. The nature of the pathologic examination has not permitted study of a quantitative relationship between the peak levels of SGO-T and the amount of infarcted muscle. All patients who died with levels of 357 to 5567 had large and extensive infarction. Patient P.W., who died with a peak level of 156, had a smaller area of infarction measuring 3 by 4 cm. We are currently attempting more quantitative estimates of the amount of infarcted myocardium in the hope of obtaining data on the relationship between the SGO-T curve and the extent of the infarct.

DISCUSSION

To date we have not observed a case of proved myocardial infarction in which the SGO-T failed to rise, provided serial blood

samples were drawn during the first 4 days of the disease. In other words, we have not found false negative tests in our series of 118 cases of proved myocardial infarction. These findings are in agreement with those of Chinsky and his associates.⁴ Others have reported false negatives with an incidence ranging from 1 to 8 per cent.^{2, 9}

False positive SGO-T tests may occur if there is associated damage to liver, kidney, skeletal muscle, pancreas, or lung. Such cases will be described in the second paper of this series.¹⁰ We cannot be certain that some of these factors were not present in all of the cases of probable and possible myocardial infarction, but in each case every effort was made to exclude them. Thus we believe that all patients with known myocardial infarction have elevation of SGO-T during the acute phase of the attack, with a decline to normal levels after 4 or 5 days. In patients suspected of myocardial infarction, elevations of SGO-T with a decline to normal levels at the expected time give indication that myocardial necrosis is indeed

present. In 7 of our 63 uncertain cases these assumptions were verified at autopsy.

The same considerations may be applied conversely to those patients who failed to show a rise of SGO-T. Those cases without a rise of SGO-T following an episode of chest pain may be considered not to have myocardial necrosis. While supporting evidence for this view is derived from animal experiments,^{5, 6} the point cannot be easily proved in man. Such proof would require a number of autopsies on patients dying of intercurrent causes shortly after attacks of anginal pain during which period the patients had been followed with serial SGO-T tests. At the present time such proof is lacking. Whether or not such patients might have small or microscopic infarcts as suggested by Sampson¹¹ must also await pathologic examination.

The data on the fatal cases strongly suggest that SGO-T levels above 350 units carry very grave prognoses and probably indicate extensive myocardial infarction.

Whether or not peak levels of SGO-T will prove to be proportional to the extent of the myocardial infarction must await more detailed study of autopsied hearts. That the problem will be difficult to solve in the human is suggested by the case illustrated in figure 8. Here there was continuous elevation of SGO-T for 10 days with peaks of SGO-T varying between 390 and 800 units. It is suggested that the volume of infarcted muscle may correlate better with the area of the time-concentration curve than with peak values of SGO-T.

SUMMARY AND CONCLUSIONS

Determinations of serum glutamic oxalacetic transaminase were made in 255 patients suspected of having acute myocardial infarction. In 111 patients the diagnosis of myocardial infarction could be established on clinical evidence and the electrocardiograms. All these patients had elevations of SGO-T, provided serial levels were obtained during the first 3 to 6 days following onset of pain. Sixty-three patients in whom the diagnosis could not be established with certainty had elevations of SGO-T similar to those seen in the proved infarctions. These were classified as probable

myocardial infarcts. Seven were proved at autopsy to have infarcts. Ten patients showed small elevations hardly out of the normal range. These were classified as possible infarcts. Seventy-one patients had no elevations of SGO-T. These were classified as angina without infarction. Of 37 fatal cases of myocardial infarction, 11 were uncomplicated by other factors. All but 1 of these 11 had peak levels of SGO-T higher than 350 units. The highest level among survivors was 336 units. Levels of SGO-T over 350 units carry a grave prognosis. The SGO-T test appears to be useful in the diagnosis of uncertain cases of myocardial infarction.

SUMMARIO IN INTERLINGUA

Determinaciones de serral transaminase glutamic-oxalacetic (SGO-T) esseva executate in 255 patientes suspecte de acute infarcimento myocardial. In 111 patientes le diagnose de infarcimento myocardial poteva esser establite super le base de datos clinic e electrocardiographic. Omne iste patientes habeva elevate nivellos de SGO-T, providite que illos esseva determinate durante le prime 3 a 6 dies post le declaration del dolores. Sexanta-sex patientes in qui le diagnose non poteva esser establite con certitude habeva nivellos elevate de SGO-T simile a lo que esseva constatate in le gruppo a infarcimentos demonstrate. Iste 66 patientes esseva classificate como casos de probabile infarcimento myocardial. Dece patientes monstrava leve elevationes que a pena excedeva le limites normal. Iste casos esseva classificate como infarcimentos possibile. Septanta-un patientes habeva nulle elevation de SGO-T. Lor casos esseva classificate como angina sin infarcimento.

In un serie de 37 casos mortal de infarcimento myocardial, 11 non esseva complicate per altere factores. Con un exception, omne le 11 habeva nivellos maximal de SGO-T que excedeva 350 unitates. Inter le superviventes, le plus alte nivello esseva 336 unitates.

Nivellos de SGO-T de supra 350 unitates rende le prognose multo grave. Il pare que le determination de SGO-T es utile in le diagnose de indecise casos de infarcimento myocardial.

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I have no great quickness of apprehension or wit which is so remarkable in some clever men, for instance, Huxley. I am therefore a poor critic: a paper or book, when first read, generally excites my admiration, and it is only after considerable reflection that I perceive the weak points. My power to follow a long and purely abstract train of thought is very limited; and therefore I could never have succeeded with metaphysics or mathematics. My memory is extensive, yet hazy: it suffices to make me cautious by vaguely telling me that I have observed or read something opposed to the conclusion which I am drawing, or on the other hand in favour of it; and after a time I can generally recollect where to search for my authority. So poor in one sense is my memory that I have never been able to remember for more than a few days a single date or a line of poetry.

Some of my critics have said, 'Oh, he is a good observer, but he has no power of reasoning!' I do not think that this can be true, for the *Origin of Species* is one long argument from the beginning to the end, and it has convinced not a few able men. No one could have written it without having some power of reasoning. I have a fair share of invention, and of common sense or judgment, such as every fairly successful lawyer or doctor must have, but not, I believe, in any higher degree.

On the favourable side of the balance, I think that I am superior to the common run of men in noticing things which easily escape attention, and in observing them carefully. My industry has been nearly as great as it could have been in the observation and collection of facts. What is far more important, my love of natural science has been steady and ardent.—CHARLES DARWIN (1809–1882).

Cardiovascular Function in Hypothermic Anesthetized Man

By JOHN C. ROSE, M.D., THOMAS F. McDERMOTT, M.D., LAWRENCE S. LILIENTHAL, PH.D., M.D., FRANK A. PORFIDO, M.D., AND ROBERT T. KELLEY, M.D.

Although hypothermia is being used as an adjunct to general anesthesia, its cardiovascular effects in man are not fully known. In this report the authors present the hemodynamic changes observed in patients undergoing hypothermia under the clinical conditions of its practical usage in the operating room. Considerable variability in vasomotor and cardiac responses was encountered, indicating that uniform behavior of patients to this agent is not to be expected in the relatively uncontrolled operating room setting; therefore, it should be used conservatively, particularly in critically ill patients in whom unexpected reactions may be disastrous.

THE use of hypothermia as an adjunct to general anesthesia is becoming increasingly common. The indications for its application, and the various technics by which patients may be cooled have been reviewed in many publications and recently summarized by Virtue.¹ However, aside from electrocardiographic studies,² measurements of the physiologic alterations produced by the artificial induction of hypothermia in man have not been made in the operating room.

With regard to cardiovascular function, it is generally assumed that those physiologic changes that occur in dogs in the controlled environment of the experimental laboratory also occur in patients in the variable atmosphere of the operating room. The work of Prec's group,³ Bigelow and his colleagues,⁴ Edwards and co-workers,⁵ and Sabiston, Theilen, and Gregg⁶ indicates that in cooled dogs, heart rate, blood pressure, and cardiac output are frequently almost linear functions of body temperature. However, Hegnauer and D'Amato⁷ have demonstrated marked elevations of cardiac output and oxygen consumption in dogs due to only moderate shivering during the cooling period.

There seemed, then, a need for more detailed observations of the circulatory alterations pro-

duced by hypothermia in man, under the conditions found in the operating room. In anesthetized patients, measurements were made in the normothermic and hypothermic state of heart rate, cardiac output, mean arterial pressure, total peripheral resistance, mean circulation time, cardiac work, central blood volume, plasma volume, and hematocrit. Measurements were made prior to any surgical procedure, and an attempt was made to exclude influences other than hypothermia, such as drugs or fluids.

MATERIALS AND METHODS

Ten patients were selected for this study. Their ages, diagnoses, preoperative drugs, and anesthetic agents used are shown in table 1. No patient had clinical evidence of cardiovascular disease. Studies were performed in the following manner:

After the induction of anesthesia and tracheal intubation, a 17-gage thin-wall needle was inserted in a femoral artery and taped in place. Rectal temperature was continuously recorded with a telethermometer.* When the patient's condition appeared stable, as evidenced by level blood pressure, pulse, and clinical depth of anesthesia, the electrocardiogram was recorded simultaneously with the direct femoral arterial pressure contour. Arterial pressures were obtained with a strain-gage transducer,† carrier-wave type amplifier and 2-channel, direct-writing oscillograph.‡ Mean pressures were determined by planimetric integration of the pulse wave.

* Yellow Springs Instrument Company, Yellow Springs, Ohio.

† P-23D, Statham Laboratories, Beverly Hills, Calif.

‡ Model 60 Twin-Viso, Sanborn Company, Cambridge, Mass.

From the Cardiovascular Research Laboratory of the Department of Medicine, and the Department of Anesthesiology, Georgetown University Medical Center, Washington, D. C.

Supported in part by a grant from the Washington Heart Association.

Dr. Rose is an Established Investigator of the American Heart Association.

TABLE 1.—Summary of Patients, Drugs and Anesthetic Agents

Patient, age and sex	Surface area (M. ²)	Preoperative diagnosis	Preoperative medication	Anesthetic* agents	Operation
D. T., 2, M	1.69	Carcinoma, esophagus	Demerol, atropine	pentothal, nitrous oxide	Resection esophagus
J. C., 40, M	1.93	Carcinoma, esophagus	morphine, atropine	pentothal, nitrous oxide	Resection esophagus
B. T., 37, F	1.46	Uterine myomata	Phenergan, Demerol	pentothal, nitrous oxide	Hysterectomy
E. F., 48, F	1.61	Carcinoma, colon	pentobarbital, morphine, scopolamine	pentothal, ether, nitrous oxide	Laparotomy
F. R., 62, F	1.78	Carcinoma, colon	pentobarbital, scopolamine	pentothal, ether, nitrous oxide	Abdomino-perineal resection
E. J., 78, F	1.54	Carcinoma, colon	pentobarbital, morphine, scopolamine	pentothal, ether, nitrous oxide	Hemicolectomy
M. W., 48, F	1.78	Carcinoma, rectum	pentobarbital, morphine, scopolamine	pentothal, cyclopropane	Abdomino-perineal resection
M. C. W., 36, F	1.45	Portal cirrhosis	pentobarbital, Demerol, scopolamine	pentothal, cyclopropane	Portocaval anastomosis
J. V., 67, M	1.86	Carcinoma, pancreas	pentobarbital, Demerol, scopolamine	pentothal, ether	Cholecystoduodenostomy
W. P., 48, M	1.80	Carcinoma, larynx	pentobarbital, morphine, scopolamine	pentothal, ether, nitrous oxide	Laryngectomy and node dissection

* All patients maintained on continuous positive pressure respirations.

Immediately following pressure recording, indicator-dilution curves were obtained with radio-iodinated human serum albumin (5 cases), T-1824 dye (2 cases), or a mixture of red blood cells tagged with Cr⁵¹ and radio-iodinated human serum albumin (3 cases).

The indicator-dilution curves were obtained following a rapid injection into an antecubital vein and femoral artery sampling, modified from the method of Werkö and his associates.⁸ Two-second blood samples were collected into paraffined tubes containing dried heparin continuously for 80 seconds following injection. Methods for chromating red blood cells, the preparation and analysis of injectates, and the analysis of blood samples for radioactivity of plasma and red blood cells have been described in a previous communication from this laboratory.⁹ Following the sample collection, rectal temperature was noted and direct pressure recording repeated. In several instances, 10 minutes following injection of indicator, a blood sample was obtained for determination of plasma volume.

The patient was then cooled by packing him with ice enclosed in cloth or plastic bags. The indwelling arterial needle was left in place. No fluids or drugs were administered during the cooling period, which averaged 2 hours in duration (range 1.0 to 2.5 hours). Although shivering was occasionally noted for brief periods during cooling, no shivering was detectable during measurement periods. At rectal temperatures between 31 C. and 32.5 C. the ice was removed and the patient dried. At this time the measurements

made prior to cooling were repeated in an identical manner, and the rectal temperature at the time of the observations was noted (table 2). After collection of a 10-minute sample for plasma volume determination, the patient was prepared for surgery.

Semilogarithmic plots of indicator concentration or radioactivity were constructed against time. The curves were analyzed by a recently described method¹⁰ and calculations made of cardiac output, mean circulation time, and central blood volume.¹¹ In 3 cases the mean circulation times of red blood cells and plasma were independently but simultaneously measured after cooling. Total peripheral resistance was expressed in peripheral resistance units¹² and cardiac work calculated by the formula of Starling and Visscher.¹³ Hematocrit values were determined in Wintrobe tubes. For plasma volume calculations, the amount of indicator injected was corrected for the amount removed in obtaining the dilution curves.

RESULTS

The measurements made and the corresponding rectal temperatures are given in table 2. Figure 1 shows graphically the results of several of the measurements.

Heart Rate. Heart rate fell significantly in 7 patients and showed no significant change in 3. The average decrease in the 7 patients was 31 per cent (range from 21 to 47 per cent). No pa-

TABLE 2.—Results of Studies in Ten Patients before and after Surface Cooling to Rectal Temperatures Shown

Patient	Rectal temperature (°C.)	Heart rate (/min.)	Stroke volume (ml.)	Cardiac output (L./min.)	Mean arterial pressure (mm. Hg)	Total peripheral resistance (P.R.U.)	Cardiac work (Kg.M./min.)	Mean circulation time (sec.)	Central blood volume (L.)	Hematocrit (%)	Plasma volume (L.)
D. T.	36.8	120	33	3.94	135	2.05	7.23*	40.0	2.63		
	31.0	80	48	3.80	101	1.57	5.22	61.3	3.95	40	
J. C.	37.0	84	67	5.60	107	1.14	8.15	36.5	3.41		
	31.0	44	54	2.39	95	2.39	3.09	58.6	2.33	45	
B. T.	37.5	88	47	4.20	81	1.16	4.63	15.4	1.08	38	2.15
	32.3	66	50	3.30	140	2.55	6.28	19.9	1.09	41	2.03
E. F.	35.6	55	51	2.80	98	2.10	3.73	37.1	1.73	38	
	30.5	50	51	2.55	77	1.81	2.36	37.8	1.61	41	
F. R.	36.4	84	56	4.71	98	1.25	6.28	30.8	2.42	39	2.71
	32.5	62	69	4.25	132	1.86	7.63	46.1	3.27	42	2.39
E. J.	36.5	68	44	2.97	115	2.32	4.65	31.0	1.54	42	
	31.0	52	50	2.62	145	3.32	5.17	46.4	2.03	47	
M. W.	36.5	60	82	4.94	70	0.85	4.70	18.4	1.51	43.5	
	31.0	60	41	2.44	90	2.20	2.99	56.8	2.31	46.5	
M. C. W.	37.4	80	53	4.21	55	0.78	3.15	31.8	2.23	38.5	2.74
	31.0	45	52	2.36	72	1.83	2.31	36.7	1.44	42	2.52
J. V.	36.3	85	46	3.95	85	1.29	4.57	35.4	2.33	35.5	4.13
	31.5	67	76	5.12	103	1.21	7.18	31.8	2.72	38	3.89
W. P.	37.0	65	70	4.58	74	0.97	4.61	33.7	2.57	41	3.85
	31.2	60	94	5.63	104	1.10	7.96	29.5	2.39	44	3.38

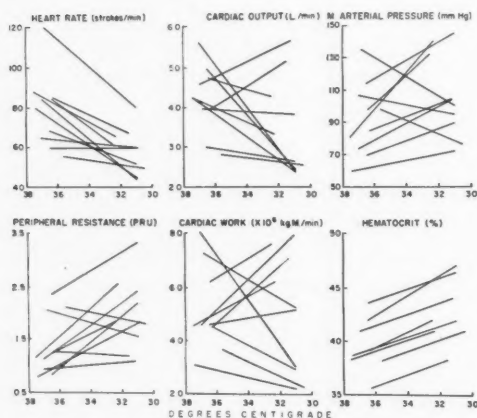
* Multiplied by 10^3 .

FIG. 1. Alterations produced by hypothermia in several hemodynamic parameters.

tient showed an increased heart rate following cooling.

Cardiac Output. Cardiac output fell significantly (more than 10 per cent) in 5 patients, at low temperatures. In these, the mean decrease was 36 per cent (range 11 to 57 per cent). In 3 cases there was a fall of less than 10 per cent (D. T., E. F., and F. R.). In 2 patients

(J. V. and W. P.) cardiac output increased significantly at low temperatures (29 and 23 per cent respectively).

Stroke volume alterations were extremely inconstant. This quantity decreased significantly in 2 cases, showed changes of less than 10 per cent in 3, and increased in 5.

Pressure Pulse Contour. The femoral arterial pressure pulse contours showed consistent alterations at low temperatures. These were primarily a prolongation of the time required for systole and a more slowly rising anacrotic limb (figs. 2 and 3).

Analysis of tracings in 6 cases with clearly defined systolic periods (onset of systole to diastolic notch) revealed an average duration of systole of 32 per cent of the total cardiac cycle (range 24 to 41 per cent) in the normothermic state. At low temperatures, the mean duration of systole increased to 39 per cent of the cycle (range 37 to 48 per cent). Similar alterations have been noted in dog aortic pressure pulse contours in this temperature range.^{14, 15}

Figure 3 illustrates the consistent finding that these alterations in pressure pulse contour

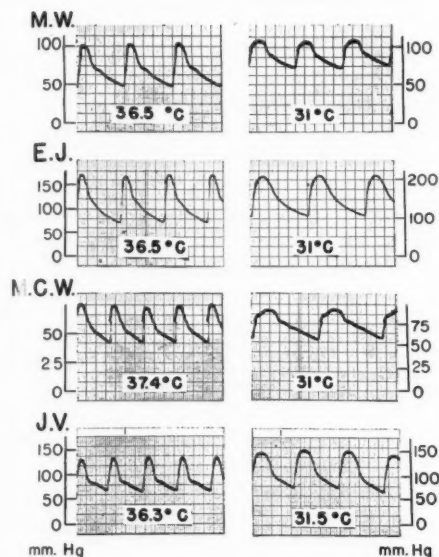


FIG. 2. Femoral arterial pressure contours in 4 cases before and after cooling. The time required for systolic ejection after cooling is prolonged.

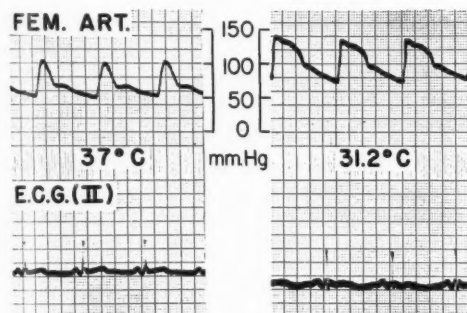


FIG. 3. Simultaneous femoral arterial pressure contour and electrocardiogram before and after cooling in W. P.

were unrelated to significant alterations in electric activity.

Mean Arterial Pressure. Mean arterial pressure rose significantly in 7 cases (mean 35 per cent, range 21 to 72 per cent) and fell in 3 (25, 11 and 21 per cent respectively in D. T., J. C., and E. F.).

Total Peripheral Resistance. These alterations were similarly inconstant. Resistance fell in 3 cases (D. T., E. F., and J. V.; 23, 13, and

6 per cent) and increased in 7 (mean 89 per cent, range 13 to 158 per cent).

Cardiac Work. Cardiac work was increased in 5 cases (mean increase 39 per cent, range 11 to 72 per cent) and decreased in 5 (mean decrease 37 per cent, range 26 to 62 per cent).

Mean Circulation Time. Mean circulation time was prolonged in 7 instances (mean prolongation 67 per cent, range 15 to 208 per cent), and shortened in 2 (J. V. 7 per cent and W. P. 12 per cent). It was not significantly altered in patient E. F.

In the 3 patients (B. T., E. F., F. R.) in whom simultaneous measurement of red blood cell and plasma mean circulation times were made, the ratio of these mean times averaged 1.05. This is higher than the 0.97 reported for normal subjects¹⁶ although the series is too small to determine a significant difference. This observation suggests that the velocity of red blood cells in relation to plasma may be decreased in the hypothermic state and requires further study.

Central Blood Volume. The central blood volume of Hamilton¹¹ theoretically includes the volume of blood contained between the site of injection of indicator and the point of sampling. This volume thus includes the great vessels, heart, and lungs, and all vessels equidistant with the sites of injection and sampling. This volume was increased by more than 10 per cent in 5 cases, decreased by more than 10 per cent in 2, and showed no significant change in 3.

Hematocrit, Plasma Volume. Precooling hematocrit levels were not determined in D. T. and J. C. The remaining 8 patients demonstrated a consistent hemoconcentration. The mean hematocrit rise following cooling was 8 per cent (range 6 to 10 per cent).

Plasma volume determinations were made in 5 instances in the normal and cooled state. All showed decreases. The magnitudes of the plasma volume alterations (6 to 12 per cent) were consistent with the hematocrit elevations, and suggest that an absolute loss of circulating plasma volume occurs in the hypothermic state. These phenomena have been well recognized in hypothermic dogs.¹⁷

DISCUSSION

This investigation has afforded the opportunity to observe the circulatory effects of induced hypothermia as it is clinically employed. The results indicate that the information obtained from the study of dogs in the experimental laboratory cannot always be "literally translated" to hypothermia in man under conditions existing in the operating room.

In anesthetized man, hypothermia produced relatively consistent changes in heart rate, mean circulation time, and the pressure pulse contour, whereas alterations in other parameters differed qualitatively. Cardiac output and mean arterial pressure, and consequently total peripheral resistance and cardiac work alterations, were unpredictable.

Differences in arterial pressure responses, chiefly hypertensive, suggest that in the temperature range studied, homeostatic vasopressor reflexes are active to varying degrees from patient to patient. In most instances, when the operation was begun, the arterial blood pressure (auscultatory method) fell to and remained at levels lower than control. However, it is impossible to draw any conclusions from this phenomenon, since the level of the blood pressure must be related to cardiac output, blood loss, "drifting" of body temperature, and the reflexes and other influences that accompany extensive surgery.

Increased cardiac output may be related to somewhat variable levels of anesthesia, resulting possibly in subclinical shivering and increased oxygen consumption.⁷

The consequences of intense systemic vasoconstriction and increased cardiac output—increased work of the heart (observed in 5 of these 10 patients)—may be deleterious. Although this is a tenuous conclusion in the absence of observations of myocardial oxygen consumption and myocardial efficiency, it warrants mention, since so-called "poor risk" patients, who, presumably, include those with heart disease, have been considered candidates for hypothermic anesthesia.¹

Controversy exists as to whether autonomic blocking agents are useful adjuncts to hypothermia.^{18, 19} The data described here may support their use. Reducing the intensity of the

vasoconstrictor response to cold might conceivably relieve considerable stress on the cardiovascular system.

Although considerable data have been accumulated regarding the physiologic effects of experimental hypothermia, there is as yet insufficient data concerning the physiologic effects of "clinical" hypothermia induced in a patient about to undergo a formidable operation. Until our understanding of the hypothermic state in man is more complete, the indications for its use should be viewed conservatively. Measurements that will contribute further to our understanding of the hypothermic state in anesthetized man include oxygen consumption, both total and regional, regional blood flow measurements, and chemical and metabolic alterations.

SUMMARY AND CONCLUSIONS

Cardiac output, direct arterial pressure contours, and other measurements of circulatory function were made in 10 patients in whom hypothermia was induced prior to extensive noncardiovascular surgery. Measurements were made before cooling and again at rectal temperatures between 30.5 and 32.5 C. The results were characterized by considerable variability. The data suggest that vasomotor and cardiac responses to cold were active to varying degrees in individual patients and that uniform physiologic responses to hypothermia cannot be expected in the experimentally uncontrolled operating room setting.

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The authors are grateful for the cooperation and assistance of Drs. George William Ware, William D. Byrne, Michael F. Lapadula, John F. Potter, Hans Eberlein, Robert C. Hill, and John A. O'Donnell, and of Miss Jean Pietras and Mr. Thomas Doyle.

SUMMARIO IN INTERLINGUA

Le rendimento cardiac, le contornos del directe pression arterial, e altere mesurationes del function circulatori esseva determinate in 10 patientes in qui hypothermia habeva essite inducite in preparation de extense intervencion chirurgic de character non-cardiovascular. Omne le determinationes esseva effectuate ante le frigidation e de novo quando le sub-

je tos monstrava temperaturas rectal de inter 30,5 e 32,5 C. Le resultados esseva caracterisado e per considerable variationes. Le datos indica que le responsas vasomotori e cardiac al effecto de frigidation esseva active a varie grados in le patientes individual e que un uniforme responsa physiologic non pote esser expectate sub le experimentalmente non-regulate conditiones del sala de operation.

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Hyponatremia associated with medical or surgical shock may be due to extra renal salt loss or deprivation and will show a decreased urinary salt concentration. Hyponatremia due to either renal tubular damage or adrenocortical insufficiency is associated with increased urinary salinity. A rapid simple test will differentiate between the 2 situations without delaying therapy. Studies to extend this observation further and to use this method to predict the reserve status of adrenal function are in progress.

KITCHELL

Vasomotor Responses in the Extremities of Subjects with Various Neurologic Lesions

I. Reflex Responses to Warming

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With the technical assistance of Dorothy Andrews, B.A.

Vascular responses to warming were studied in hemiplegic patients and after sympathectomy, using venous occlusion plethysmography of foot and leg. Comparisons were made with corresponding age groups. The pattern of response was essentially unchanged in hemiplegic patients, but was altered substantially where sympathetic pathways had been interrupted.

DURING the course of studies concerned with responses of various vascular beds to physiologic and pharmacologic stimuli, it became apparent that the responses evoked in human limbs that had been deprived of their sympathetic innervation were of considerable interest. For purposes of comparison, it seemed advisable to study also the behavior of the vascular response of paralyzed extremities in patients following cerebral vascular accidents and transection of the spinal cord. The present paper describes some of the abnormal vascular responses encountered in a study of these neurologic disorders.

Sympathectomy

A number of workers have studied the altered vasomotor responses after sympathectomy. Usually consistently elevated basal flow was described after sympathectomy.¹⁻⁵

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However, reports have varied as to the changes in response to vasodilator and vasoconstrictor stimuli. Goetz⁶ found that flow to the toe did not respond to either constrictor or dilator stimuli after sympathectomy and that in some cases blood flow was decreased in response to vasodilator stimuli and increased in response to vasoconstrictor stimuli. Mendlowitz and Touroff⁷ found the responses to vasodilator stimuli to remain directionally the same after sympathectomy. Prinzmetal and Wilson,⁸ in 1936, tested 2 patients with Raynaud's disease before and after sympathectomy. These patients showed an increase in blood flow to the forearm in response to the Gibbon-Landis procedure before sympathectomy, but after operation a decrease in blood flow was observed. In earlier work, however, Grant and Holling⁹ had found that after sympathectomy a human forearm exhibited an increase in blood flow in response to body warming. Wilkins and Eichna,¹⁰ in 1941, studied vasomotor reactions to ice, pin prick or pinch, deep breath, immersing a hand or foot in very cold or very hot water, exercise, loud noise, and mental arithmetic. They found marked changes in flow in the nonsympathectomized extremity and occasionally also some changes in the sympathectomized one; the latter, however, correlated with changes in blood pressure. Duff and Swan,¹¹ in 1951, and Barcroft and Swan¹² measured blood flow to the calf and forearm in sympathectomized human extremities during infusion with epinephrine; they reported an initial rise to 2 to 3 times the resting level returned to the

baseline during the infusion. In contrast, in nonsympathectomized limbs there was some decrease after this initial rise, immediately followed by another rise that was sustained throughout the infusion. These authors could not correlate the changes in blood flow with changes in blood pressure. Still more recently, Ahmad¹³ reported a case of hyperhidrosis with homolateral sympathectomy in whom local warming of the sympathectomized hand to 41 C. caused vasoconstriction, while the normally innervated hand responded with vasodilation.

Hemiplegia

As long ago as 1888, Gowers¹⁴ encountered some interesting circulatory phenomena while studying cases of hemiplegia. The paralyzed extremities showed no change, an increase in skin temperature and coloring, mostly in the early stages, or a decrease in skin temperature associated with pallor, followed later by cyanosis. He found the same type of disturbance in traumatic lesions of the central gyrus that was "frequently accompanied by vasomotor disturbances in the contralateral extremity." He believed that destruction of subcortical vasomotor centers caused increase in blood flow, while "irritation" of these centers had the opposite effect. Uprus and co-workers¹⁵ (1935) found no consistent difference in temperature between the 2 sides of patients with hemiplegia; there was likewise no difference in reflex responses to vasomotor stimuli, except in the rate of cooling. In the same year, Sturup and associates¹⁶ reported that response to vasoconstrictor stimuli in patients with lesions of the cerebral hemispheres did not differ from the normal. On the other hand, Ellis and Weiss¹⁷ demonstrated in 1936 that the circulation of the hemiplegic limb was increased and might remain increased for as long as 13 years after a cerebrovascular accident.

Spinal Cord Transection

Guttmann and Whitteridge¹⁸ observed the reflex responses to distention of the bladder in patients with transection of the cord. While patients with low transection responded with vasoconstriction in the toes and "compensatory" vasodilation in the fingers, patients

with high lesions responded with vasoconstriction in both the upper and lower extremities. Pollock and co-workers¹⁹ observed what they called "defects in regulation of heat production, sweat and vasoconstriction" in patients with spinal cord lesions. They believed these defects to be due to interruption of "impulses from suprasegmental levels." In 1953 Armin, Grant, and co-workers²⁰ demonstrated increased reactivity to vasoconstrictor stimuli in the denervated rabbit's ear and referred to a similar phenomenon in the human finger after sympathectomy. They believed, on rather incomplete evidence, that this is due to interruption of fibers that normally act as dilators through release of acetylcholine.

In view of the conflicting evidence, it was considered worthwhile to restudy the respective roles of cerebrospinal and sympathetic innervation in regulating blood flow to the human extremities. The present report deals with the reflex response to warming the body.

METHOD AND MATERIAL

All experiments were done at a constant temperature of 20 C. ($\pm 0.5^\circ$) and 55 per cent humidity with an air current of less than $4\frac{1}{2}$ feet per minute. Such environment provides a mild vasoconstrictor stimulus for testing the vasodilator response to the Gibbon-Landis procedure.²¹ The subject was in the basal state, clad in cotton pajamas with hands and feet exposed. Blood flow was measured plethysmographically.²² Surface temperature was recorded quasi-continuously on a 6-channel Leeds and Northrup Speedomax. The subject was considered "adapted" to the environment when the toe temperatures had remained constant for at least half an hour.

Twelve hemiplegic patients, 4 patients with "high transection" of the cord, and 8 patients with 11 sympathectomized limbs have been studied. Comparisons were made with studies in 10 young normal persons, 9 elderly subjects (50 to 75 years) without demonstrable vascular disease, and 8 patients with obliterative arteriosclerosis. Hemiplegic limbs were also directly compared with their nonparalyzed fellows in 5 patients, and the sympathectomized with the nonsympathectomized side in 4 patients. All experiments were repeated and the observations were relatively reproducible.

RESULTS

Hemiplegia

Basal flows in limbs of hemiplegic patients were within the range of those in elderly sub-

TABLE 1.—Influence of Gibbon-Landis Procedure on the Blood Flow of the Lower Extremities, (ml./100 cc. tissue/min.)

Patient	Basal flow	Maximum response	Patient	Basal flow	Maximum response
Subjects without demonstrable vascular disease					
20-40 years			50-80 years		
I.W.	13.6	17.7	F.K.	3.6	5.9
S.D.	9.1	18.0	W.F.	3.4	6.5
S.L.	3.2	7.0	H.T.	10.5	12.1
M.H.	24.0	25.4	J.J.	8.4	14.2
D.S.	20.9	30.5	J.B.	8.6	10.1
E.C.	10.5	14.8	J.H.	15.9	22.7
A.O.	16.0	21.6	M.S.	10.5	14.8
S.P.	16.7	18.9	J.F.	5.7	9.9
A.S.	14.5	24.4	E.V.	8.3	12.2
E.G.	9.4	20.8			
Average	13.8	19.9	Average	8.3	12.0
Elderly patients with obliterative vascular disease			Hemiplegic patients		
R.K.	2.8	6.9	M.N.	6.7	8.5
J.C.	2.0	3.9	M.S.	4.3	7.2
J.K.	2.3	3.2	L.J.	8.4	12.3
M.E.	3.2	9.7	M.G.	6.7	10.0
M.G.	4.4	6.2	E.P.	16.6	35.5
M.N.	2.3	4.9	M.E.	3.9	4.3
C.B.	2.8	5.1	E.H.	10.7	15.5
A.D.	6.0	9.4	A.R.	6.4	10.0
			C.J.	5.5	7.1
Average	3.2	6.2	M.M.	10.2	15.3
			S.T.	13.6	25.7
			C.C.	4.1	4.5
			Average	8.1	13.0

jects of comparable age without demonstrable vascular disease, while young adults had a much higher average flow (table 1). In response to the Gibbon-Landis procedure, hemiplegic limbs showed an increase in blood flow comparable to that observed in a control group of similar age (table 1). In 5 hemiplegic patients the paralyzed limbs were compared with the nonparalyzed fellows. Here the basal blood flow appeared to be generally lower in the nonparalyzed than in the paralyzed limb (table 2). One example is shown in figure 1.

The subjects with obliterative arteriosclerosis reacted directionally in a similar fashion to the other 3 groups, but the initial flows as well as the maximal flows were lower. This fact was

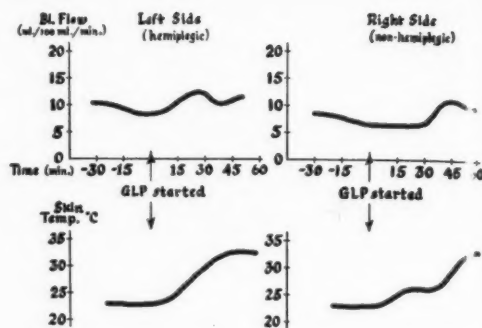


FIG. 1. Response to Gibbon-Landis procedure, L.J., 44, female.

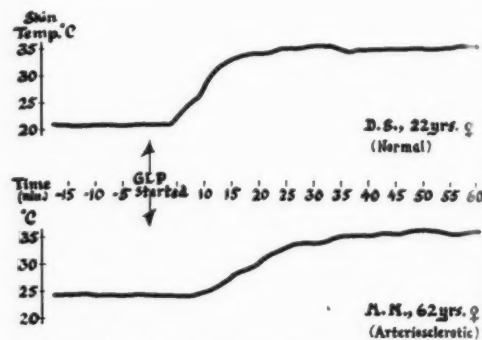


FIG. 2. Skin temperature response to Gibbon-Landis procedure.

not expressed in the measurement of surface temperature, which eventually reached essentially the same values as in the other control groups, although increase was delayed in starting and proceeded at a much slower rate (fig. 2). There is then no qualitative difference in the reflex vasodilator response in these 4 groups (table 1) with intact sympathetic innervation.

Spinal Cord Transection

In the patients with "high transection" of the cord, the average basal blood flow in the paraplegic limbs was higher than in the arteriosclerotic patients but lower than in the other 2 control groups. Reflex vasodilator responses varied (table 3). In response to the Gibbon-Landis procedure the blood flow in the first of these 4 subjects decreased markedly, in 1 it increased markedly, while in the other 2 it

TABLE 2.—Influence of Gibbon-Landis Procedure on the Blood Flow of the Lower Extremities in Hemiplegic Patients, (ml./100 cc. tissue/min.)

Patient	Duration of hemiplegia (at time of study)	Paralyzed side		Nonparalyzed side	
		Control reading	Maximum response	Control reading	Maximum response
M.N.	8 months	6.7	8.5	2.3	4.9
M.S.	2½ months	4.3	7.2	2.4	3.6
L.J.	3 weeks	8.4	12.3	6.7	10.3
M.G.	3 months	6.7	10.0	4.4	6.2
E.P.*	11 years	16.6	35.5	8.3	14.4
Average		8.5	14.7	4.8	7.9

* This patient is hypertensive.

TABLE 3.—Influence of Gibbon-Landis Procedure on the Blood Flow of the Lower Extremities in Sympathectomized and Paraplegic Patients, (ml./100 cc. tissue/min.)

Patient	Basal flow	Maximum response
Sympathectomized patients		
A.B.	12.6	8.6
F.B.	5.25	6.0
L.S. (R)	4.45	1.6
L.S. (L)	4.4	3.5
A.F. (R)	9.4	6.5
A.F. (L)	12.9	9.2
S.Q.	10.3	10.0
H.M. (R)	15.7	14.8
H.M. (L)	17.2	6.3
Average	10.2	7.4
F.K.*	14.7	10.7
A.M.†	18.1	10.7
Average	16.4	10.7
Paraplegic patients		
A.R.	7.1	1.4
D.J.	7.0	6.8
J.R.	5.6	17.1
S.P.	6.1	7.5
Average	6.5	

* No peripheral arterial disease. Sympathectomized for "cold feet."

† No peripheral arterial disease. Sympathectomized for hypertension.

showed little change. The diversity of response in these patients may well be due to differences in location and extent of the transection. The first patient was the only one in whom the

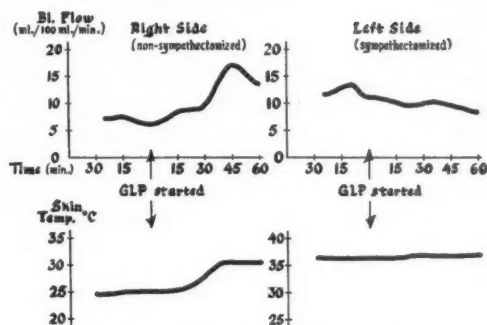


FIG. 3. Response to Gibbon-Landis procedure, A.B., 47, male.

transection was radiologically proved to be above T₅.

Sympathectomy

The reflex responses to warming in sympathectomized limbs were of considerable interest. Eight patients were studied and in 3 of these measurements of blood flow were carried out in both sympathectomized limbs. Six of these 8 patients were sympathectomized for occlusive arterial disease, 1 for hypertension and 1 simply for "cold feet." Thus 11 sympathectomized limbs were studied. Seven of these 11 limbs (table 3) responded to the vasodilator stimulus with a significant decrease in blood flow. In the sympathectomized limb initial basal flow and surface temperature are, of course, higher than in the nonsympathectomized fellow. Average basal flows were higher in limbs sympathectomized for vascular disease than in a comparable nonsympathectomized group (compare tables 1 and 3). Two patients who had been sympathectomized in the absence of occlusive vascular disease likewise had higher basal flows than their young control group (compare tables 1 and 3). In response to the Gibbon-Landis procedure blood flow increased as usual on the nonsympathectomized side, but decreased on the sympathectomized side (fig. 3). Surface temperature rose in the normally innervated limb, reflecting the increase in blood flow, but did not fall with the decrease in blood flow on the sympathectomized side.

DISCUSSION

Changes in blood flow through a part of the body or an organ of the body are generally con-

sidered to be expressions of vasomotor impulses. The results presented here then seem to indicate that cerebral lesions causing hemiplegia do not essentially alter the reflex vasodilator response (increase in blood flow) to warming, in either the hemiplegic or the unaffected extremity.

There was no correlation between basal flow and the degree of discoloration. A cursory study of possible changes in the minute circulation by capillary microscopy at the fingernail bed did not reveal any conclusive difference between the 2 sides except in those cases that showed hemi-edema: in the presence of hemi-edema there was blurring of the outline of the capillary loops.

The reflex vasomotor responses to a dilator stimulus in the 4 paraplegic subjects with alleged high transection of the cord varied from patient to patient. It is noteworthy that the only patient with radiologically proved traumatic transection at a level apparently just above T_6 was the only one in whom a decrease in blood flow was observed in response to the Gibbon-Landis procedure. In the other 3 patients the evidence either for the exact level of lesion or for the completeness of transection of the cord is insufficient. It seems probable that the degree of alteration of vasomotor responses depends upon the level as well as the completeness of transection. The variability of response in these 3 patients suggests that as these studies proceed, the type of response might prove to be an indication of the location and extent of the lesion. It has generally been taught that sympathetic pathways to the lower extremities leave the spinal cord not higher than T_{6-6} .²³ It is also usually assumed that abolition of sweating is evidence for complete sympathetic denervation.²⁴ All 4 of the patients reported here showed complete absence of perspiration of the lower extremities tested by the Guttman procedure,²⁴ but their vasomotor responses varied. Further investigation may bear out previously expressed doubt as to the acceptability of loss of perspiration as proof of complete sympathetic denervation.^{25, 26}

The results, however, of studies on surgically sympathectomized patients are quite clearcut. In none of the limbs studied after sympathec-

tomy could an increase in blood flow be produced reflexly by warming; in the majority of instances the opposite response, a decrease in blood flow, was observed. The regularity with which these carefully sympathectomized limbs fail to respond to a vasodilator stimulus suggests that this procedure might be useful as a test for completeness of sympathectomy.

The physiologic events that lead to alterations in vasomotor responses in limbs that have been deprived of most of their sympathetic innervation are still obscure. Systemic arterial pressure bears no demonstrable relationship to the changes in blood flow produced by the Gibbon-Landis procedure. In a person who has undergone unilateral sympathectomy, there is, in response to the Gibbon-Landis procedure, an increase in blood flow on the non-sympathectomized side and simultaneously a decrease on the sympathectomized side; the increase on the nonsympathectomized side is not in excess of that observed in controls. In bilaterally sympathectomized subjects, a decrease in blood flow usually occurs on both sides in response to warming. It appears unlikely, therefore, that a "borrowing-lending mechanism"²⁷ could explain the vasomotor responses.

Preliminary observations suggest the possibility of influencing toward normal reflex vasomotor responses in sympathectomized limbs by adrenergic blockade. This effect could be interpreted as indicating an active role of catechol amines.

Epinephrine and norepinephrine are released from the adrenal gland in response to hypothalamic stimulation.²⁸ Such stimulation may be effected by warming of the blood, as in the Gibbon-Landis procedure. "Sensitization" of sympathectomized organs to the action of circulating catechol amines has been demonstrated in the basic work of Cannon and his associates²⁹⁻³² and later workers³³ in animals. This work was applied to man as early as 1934.³⁴ Some of the evidence presented later^{35, 36} has not been entirely convincing.

Evidence that norepinephrine is liberated locally in the arterial wall has been reported³⁷ Burn and co-workers³⁸ demonstrated the destruction of norepinephrine by amineoxidase

and showed that the rate of destruction can be slowed considerably by inhibiting the enzyme. It might be speculated then that the sympathetic supply influences the liberation of the catechol amines or its enzymatic destruction. If this is the case, it is still necessary to explain why such action appears to operate only when vasomotor stimulus is applied.

Increase in blood flow is generally followed by a rise in skin temperature but decrease in blood flow in response to the Gibbon-Landis procedure after sympathectomy is not necessarily accompanied by a fall in surface temperature. This poor correlation between skin temperature and blood flow confirms the previous report of Hoobler and co-workers²⁶ and helps define the limits of usefulness of measurements of skin temperature as an index of blood flow to the extremity.

SUMMARY

The vasomotor responses to the Gibbon-Landis procedure (reflex response to warming) were studied in hemiplegic patients, subjects with "high transection" of the cord, and in sympathectomized patients. The response in hemiplegic patients was vasodilator in nature just as in the 3 control groups (young normal subjects, elderly subjects without demonstrable vascular disease, and patients with arteriosclerosis). One patient with documented transection of the cord above T₈ behaved like subjects after surgical sympathectomy. The differences in response in 3 other paraplegic patients may be due to differences in location and extent of their cord lesions. Basal blood flow was higher in sympathectomized limbs than in comparable controls. Of 11 sympathectomized limbs tested for vasodilatation in response to the Gibbon-Landis procedure, 4 showed no response, while 7 responded with decrease in blood flow (vasoconstriction).

SUMMARIO IN INTERLINGUA

Le responsas vasomotori evocate per le manipulation de Gibbon-Landis (responsa reflexe a calefaction) esseva studiate in patientes hemiplegic, in subjectos con "alte transection" del medulla spinal, e in patientes sympathectomizzate. In patientes hemiplegic, le

responsa esseva de natura vasodilatatori, exactemente como in le individuos del tres gruppos de controlo (juvene subjectos normal, plus vetule subjectos sin demonstrabile morbo vascular, e patientes con arteriosclerosis). Un patiente con documentate transection del medulla spinal supra T₈ se comportava como le subjectos con sympathectomia chirurgic. Le differentias del responsas in tres altere patientes paraplegic es possibilmente causate per differentias del sito e del grado de lor lesiones spinal. Le basal fluxo de sanguine esseva plus alte in extremitates sympathectomizzate que in comparabile casos de controlo. In un serie de 11 extremitates sympathectomizzate, tests del vasodilatation in responsa al manipulation de Gibbon-Landis esseva negative in quatro casos, durante que septe casos respondeva per un reduction del fluxo de sanguine (vasoconstriction).

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Bacterial Endocarditis Following Cardiac Surgery

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Intracardiac surgery for rheumatic and congenital heart disease entails direct trauma to both normal and abnormal endocardium. This communication inquires into the incidence and nature of the endocardial infections that develop subsequent to this injury. On the basis of an examination of 2,263 patients operated upon for acquired and congenital heart disease during a 5-year period terminating in November 1955, bacterial endocarditis appears to be an infrequent complication of surgery, is caused by organisms not so commonly encountered in unoperated patients, and is characterized by a clinical pattern quite different from that ordinarily associated with bacterial endocarditis. The rate of attrition in this group of patients is high, and unquestionably is related to the antibiotic resistance of the unusual organisms and the severity of the basic heart disease.

IN THE era before cardiac surgery, bacterial endocarditis generally involved endocardial or endothelial structures rendered abnormal by disease or congenital variation, although occasionally it arose on normal structures and pursued a more virulent course. Surgery on the interior of the heart produces a type of acute endocardial injury, both in normal portions of the endocardium and in the area of chronic disease to which the surgery is directed. It should, therefore, not be surprising to find instances of infection of the endocardium after cardiac operations. However, with the advance of cardiac surgery, the occurrence of bacterial endocarditis has not been frequently reported.

Nevertheless, it has been a tragic, if uncommon, event in a large series of surgical cases. It was, therefore, considered worthwhile to review our experience with bacterial endocarditis following such surgery, and to compare these cases with the much larger group undergoing similar operations in the last 5 years, but without this complication.

According to White's estimate,¹ before the application of surgery to heart disease, subacute bacterial endocarditis made up 1 to 2 per cent of all types of cardiac disease. The incidence was noted to be quite high in the age group 20 to 30,^{2, 3, 7} and rheumatic valvular disease was stressed as the background for the development of bacterial endocarditis.^{2, 17} While pure mitral stenosis is rather rarely the under-

lying lesion,⁴ a combination of mitral stenosis and insufficiency is quite frequent. In the series of 408 cases of Gates and Christie,³ the mitral valve alone was affected in 169 cases, the aortic valve solely in 49 instances, both aortic and mitral valves in 145 cases, while in 45 congenital heart disease was the basic lesion. The occurrence of tricuspid or pulmonary valve infection is rare.⁵ When the right side of the heart is affected, it is almost always in association with a left-sided endocarditis or with a congenital abnormality.^{6, 7}

In the era prior to cardiac surgery, the importance of the *Streptococcus viridans* was evident. Christian² reported 150 cases due to this organism, 4 to *Staphylococcus albus*, 2 to unidentified staphylococci, and 1 to a pleomorphic bacillus. Morrison⁵ and Middleton and Burke⁷ gave similar, if not quite so overwhelming figures.

With the advent of cardiac surgery, reports of bacterial endocarditis have appeared, first in patients with congenital defects, later in patients operated upon for acquired valvular heart disease. In a report of 1,000 patients operated upon for the tetralogy of Fallot, by systemic-pulmonic anastomosis, Taussig and associates,⁸ stated that 17 of 844 who survived surgery developed bacterial endocarditis after surgery, and that 4 died of this complication. The onset of infection in 11 patients was soon after surgery; in 6 others, more than 2 months afterwards. They assumed that the infection occurred at the site of anastomosis, but autopsy was performed in only 2 late cases, and the infection was not proved in 1. In the other case,

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nothing was stated about the site of the infection. They implied that the higher incidence in the early postoperative period was due to infection at the line of suture before it had healed, but stated that the risk of illness after 2 months was no greater than in unoperated patients. Two case reports^{9, 10} with autopsy findings, 2 and 2½ years, respectively, after Blalock operations, showed no infection of the artificial ductus, but involvement of the pulmonary and tricuspid valves and a mycotic aneurysm of the pulmonary artery.

Of 273 cases operated on for patent ductus arteriosus, reviewed by Scott,¹¹ only 1 developed bacterial endocarditis, the febrile episodes appearing 6 months after surgery. Autopsy revealed an aneurysm of the ductus and recanalization with infection.

A few case reports have appeared describing

infection following mitral commissurotomy, and all of these, where the organism was recovered, were due to penicillin-resistant staphylococci,¹⁴⁻¹⁶ except 1 that was due to a pseudomonas.¹² In 1 instance all cultures were sterile.¹³ The interval between surgery and the onset of the illness was reported as 7 to 21 days in most of these, but 1 case of Dalton, Williams and Atkins¹⁶ occurred 2 months, another 3½ months after operation. These authors are the only ones reporting incidence in a large surgical group (3 cases in 150 operations). In the cases reported by these various authors, only 2 recovered. Vegetations on the mitral valve were found at autopsy in 4 of the other 5 cases.

MATERIAL

Cases of valvular heart disease subjected to cardiac surgery in the 5 years prior to November 1,

TABLE 1.—Clinical and Bacteriologic Data in Twenty Cases of Bacterial Endocarditis

Sex	Age range	Heart rhythm	Valve calcification	Valve lesion or congenital defect	Operation	Interval after surgery	Organism
Male 14	30-51	11 NSR* 3 AF	10 yes 3 no 1 not determined	6 AS (1 with ai)† 4 AI (2 with AS, 1 as, ms, mi) 1 MS (with mi) 3 MS, AS (2 with ai, 1 with mi)	6 TAAC‡ 2 TAAC and NP 1 NP 1 NAAL 1 MC 2 MC and TAAC 1 MC and TVAC	4 10 days or less 4 More than 10 days but less than 3 months 5 3 months or more 1 Not known	7 CNS§ 1 CPS 2 SV 2 EC 1 NHS 1 ?
Female 6	27-51	5 NSR 1 AF	1 yes 4 no 1 not determined	2 MI (both with ms) 3 MS 1 ASD	1 MSu and MC 1 TVPT 3 MC 1 ASP	1 10 days or less 2 More than 10 days but less than 3 months 3 3 months or more	2 CNS 2 CPS 2 SCND

* NSR—normal sinus rhythm; AF—atrial fibrillation.

† AS—major aortic stenosis; as—minor aortic stenosis; MS—major mitral stenosis; ms—minor mitral stenosis; AI—major aortic regurgitation; ai—minor aortic regurgitation; MI—major mitral regurgitation; mi—minor mitral regurgitation; ASD—atrial septal defect.

‡ TAAC—Transaortic commissurotomy; TVAC—Transventricular aortic commissurotomy; NAAL—Nylon aortic annulus ligature; NP—Nylon peduncle; MC—Mitral commissurotomy; MSu—Mitral suture; TVPT—Transventricular pericardial tamponade for MI; ASP—atrioseptopexy.

§ SV—*Streptococcus viridans*; EC—*Enterococcus*; NHS—Nonhemolytic streptococcus; CNS—Coagulase negative staphylococcus; CPS—Coagulase positive staphylococcus; SCND—*Staphylococcus coagulase not determined*; ?—Not known, lesion found at autopsy.

955, were reviewed. Of 1,889 cases, 1,159 were pure mitral stenosis, 155 pure aortic stenosis, 142 major mitral regurgitation, 33 major aortic regurgitation, and 119 combinations of aortic and mitral stenosis. The remaining 281 were varying combinations of stenosis and regurgitation at 1 or more valves. In addition, 374 cases of congenital heart disease were operated upon. The usual clinical and bacteriologic criteria for bacterial endocarditis were fulfilled by all cases included in this report, except 1 discovered at autopsy. The interval between surgery and the onset of infection was considered to be the time elapsed between the date of operation and the onset of the fever during which positive blood cultures were obtained.

RESULTS

The pertinent clinical and bacteriologic findings are summarized in table 1. Altogether, 20 cases of bacterial endocarditis occurred prior to November 1955. The aortic valve was the one most frequently the site of prior disease in the patients who developed this infection.

Calcification was commonly present in the whole group, especially in the aortic valves. The operative procedures performed were mostly those designed to correct the aortic valvular lesion, either stenosis or regurgitation or both. The cases were about evenly divided, as to the postsurgical interval before the clinical appearance of the endocarditis, among an early period (less than 10 days), an intermediate period (10 days to 3 months), and a late period (3 to 10 months). The most important infecting organism was the staphylococcus, generally the coagulase-negative variety.

Information about the sensitivity of the organism to antibiotics was available in 15 of the 20 cases (table 2). In general the staphylococci were resistant to penicillin and showed the greatest sensitivity to carbomycin (Magnamycin) and chloramphenicol (Chloromycetin). The streptococcus viridans and the entero-

TABLE 2.—Sensitivity of the Infecting Organisms

Organism	No. tested	Penicillin	Streptomycin	Magnamycin	Chloromycetin	Terramycin
Staphylococcus						
Coagulase positive	3	3 Resistant	2 Resistant 1 Sensitive	2 Resistant 1 Not determined	2 Resistant 1 Sensitive	2 Resistant 1 Sensitive
Coagulase negative	9	6 Resistant 1 Moderately sensitive 2 Sensitive	6 Resistant 2 Moderately sensitive 1 Sensitive	1 Resistant 1 Moderately sensitive 6 Sensitive 1 Not determined	2 Resistant 2 Moderately sensitive 5 Sensitive	7 Resistant 2 Sensitive
Coagulase not determined	1	1 Sensitive	1 Resistant	1 Not determined	1 Resistant	1 Resistant
Streptococcus	2	1 Resistant (enterococcus) 1 Sensitive (<i>S. viridans</i>)	2 Resistant	1 Not determined 1 Sensitive	1 Sensitive 1 Resistant	2 Resistant

Sensitivity was determined on blood agar plates with filter paper disks saturated in antibiotic solutions.

Penicillin, 50 U./ml.:	Sensitive:	Zone of inhibition greater than 20 mm. diameter
	Moderately sensitive:	Zone of inhibition 15 to 20 mm. diameter
	Resistant:	Zone of inhibition less than 10 mm. diameter
Streptomycin, Magnamycin, Chloromycetin, Terramycin, 500 U./ml. each:	Sensitive:	Zone of inhibition greater than 15 mm. diameter
	Moderately sensitive:	Zone of inhibition 10 to 15 mm. diameter
	Resistant:	Zone of inhibition less than 10 mm. diameter

coccus showed the expected sensitivity and resistance respectively to penicillin.

Information concerning the therapy was available in 17 patients (table 3). It was not practical to analyze the dosage, duration, or method of administration in this small series, because of their great variation. Most of the patients were seriously ill, and changes were made in all aspects of therapy in accordance with the clinical response of the patient, rather than any arbitrary rules of management. For this same reason a number of patients were

treated with a considerable variety of antibiotics.

Table 3 also shows the over-all mortality in relation to the infecting organism. It is not always possible to be sure that any given patient died as the result of his infection. One patient (case 7), who was free of fever for nearly 18 months and died of heart failure, might be included in the recovered category, particularly since it is believed that he could well have died of heart failure at this time even if he had never had bacteremia. One patient (case 19), who appeared clinically cured when last seen and who died 6 months later of an unknown cause, is listed under those dead of the disease. One of those listed as dead (case 13) was reported at autopsy in another hospital to have miliary tuberculosis, with tubercle bacilli and staphylococci clustered together on the strip of pericardium used to suture the mitral valve; it is doubtful that she died of bacterial endocarditis as such. A fourth patient (case 3) appeared to recover, but had a febrile relapse 2 months after the end of therapy to the time of his death. He succumbed while undergoing surgery for an infected retroperitoneal hematoma, diagnosed clinically as a mycotic aneurysm of the left iliac artery. In general, it is apparent that the mortality rate is high for the coagulase-negative staphylococci, less so for the other organisms.

Five of these patients came to autopsy at our institution. The aortic valve was the only site of the endocarditis in 3 cases (2, 5, and 18) and the mitral valve in 1 case (13). Both the aortic and tricuspid valves were involved in case 20.

The cardiac rhythm at the time the infection appeared was normal in 16 cases and atrial fibrillation in 4. This incidence is undoubtedly partly the result of the preponderance of aortic lesions in this group of 20 cases. It may also be a reflection of the old dictum that bacterial endocarditis is uncommon in atrial fibrillation.

DISCUSSION

The well-known tendency of bacterial endocarditis to seek out the aortic valve in non-surgical cases is also manifest in the surgical

TABLE 3.—Therapy and Results

Organism	Penicillin	Streptomycin	Magnamycin	Chlormycetin	Aureo-or Tercamycin	Therapy not known
Staphylococcus			15		15	
Coagulase positive (3 cases)	20		16 20			
Coagulase negative (9 cases)	2* 3# 5 7° 10 14 18	3 5 7 10 14	2 7 7 10	2 7	5 7 14	6
Coagulase not determined (2 cases)	19†¶ 9‡	19	19 9	19 9	19 9	13
Streptococcus (5 cases)	1 8 11 17	11 17		17	17	4
Organism not known (1 case)	12§	12				

Numbers refer to the case number. Those in **bold type** represent survivors.

* Also Bacitracin.

† Also Erythromycin and Achromycin.

‡ Also sulfadiazine and Erythromycin.

§ Autopsy showed endocarditis.

|| Autopsy also showed miliary tuberculosis.

¶ Recovered on leaving hospital; died 6 months later of unknown cause.

Apparent recovery; death from relapse with mycotic iliac aneurysm.

° Recovery from endocarditis; died 18 months later of heart failure.

group here reported. Thus, of the 150 cases of pure or major aortic stenosis, 6 developed this disease. Even more striking is the incidence in surgically treated cases of aortic regurgitation, 4 of 33 developing infection. This incidence may be related to the use of foreign material (especially Nylon) at operation. On the other hand, of 1,159 cases of pure mitral stenosis, only 4 are known to have become infected after surgery. There is an intermediate incidence of the disease in the other 2 large groups that came to surgery, 3 in 400 cases of combined aortic and mitral stenosis or varying combinations of such stenosis with minor regurgitation, and 2 in 142 cases of major mitral regurgitation.

It cannot be stated that these results represent a higher incidence of this disease than could be expected if surgery had not been performed. One would have to know what the expected occurrence of the disease would be in a 3-month or 6-month period of the life of a group of similar patients (similar in age, sex, location and degree of valvular disease) not undergoing cardiac surgery, or even a group of similar patients undergoing some other form of surgery. Such data are not at hand. The only information now available is from autopsy material that tells us the rate of occurrence in the lifetime of a group of patients, now dead, not in an isolated 3 to 6-month segment of that lifetime, as we learn from our surgical material.

It should be remarked that the incidence of bacterial endocarditis is relatively low in cases of atrial septal defect, and yet we have seen 1 case in 82 operated patients.

Perhaps the influence of calcific masses in the valvular structure is similar in some ways to the influence of foreign material on the course of the disease. Such areas of calcification are largely avascular, and at times the calcium erodes through the endocardial surface of the valve, producing a rough surface on which it is possible for a fibrin nidus to form and for bacteria to grow. This development may be a factor in the greater incidence of the disease at the aortic valve, where calcification is greater in frequency and amount than at the mitral valve.

The onset of the infection occurred fairly quickly in one third of the cases, moderately quickly in one-third, and slowly in another one-third. Yet, the possible causal relationship to surgery cannot be denied even in the last group, except perhaps in 2 cases that appeared 7½ months and 10 months after surgery. There can be no arbitrary time limit beyond which the disease can be said to be unrelated to surgery. Rather, one can say only that the longer the interval between surgery and clinical evidence of infection, the less likely is there a causal relationship. The insidious onset of the disease makes any other conclusion subject to considerable error.

The etiologic agent was not the usual streptococcus viridans, but rather the staphylococcus, most frequently coagulase-negative. Certainly the clinical picture was not characteristic of bacterial endocarditis of a subacute nature, since petechiae were never seen, nor was clubbing of the fingers, Osler's nodes, or a café-au-lait color. A palpable spleen was most uncommon. All in all, one is forced to conclude that these infections differ from the commonly accepted pattern of subacute bacterial endocarditis in nonsurgical cases. Embolism was seen in only 1 case.

In 1 case with a staphylococcus cultured at autopsy, tubercle bacilli were observed on the strip of pericardium used to obstruct the mitral valve orifice. In addition, there were healed vegetations on this same tissue, presumably due to another organism. Finally, there was generalized miliary tuberculosis of the lung, pericardium, liver, spleen, kidney, and periaortic nodes, suggesting the possibility of tuberculous endocarditis.

In accordance with recent experience, we have observed penicillin resistance in some staphylococci. Eight of 12 organisms were distinctly resistant to this antibiotic, and also to streptomycin and oxytetracycline (Terramycin). In a general way these organisms were found somewhat sensitive to Chloromycetin and erythromycin. Sensitivity studies on streptococci are too meager to permit any conclusions. Most patients received large doses of antibiotics prior to and in the 10-day period after surgery. This antibiotic program

always included penicillin, so that one could expect to grow in mouth, bowel, bladder, and bloodstream only those organisms that were able to survive such therapy and become established. If this theory is correct, the need for a "light hand" in the handling of antibiotics is emphasized for this group of patients. Consistent with this thought is the observation of a number of patients with pseudomonas bacteremia after surgery. This organism may be one of a group that would be released for growth when its potential antagonists had been abolished by vigorous antibiotic therapy.

If care not to use too much is important in prophylaxis against the development of resistance, care to use enough or more than enough, is important in the management of the case with a positive blood culture. Initially we thought it wiser to begin therapy with the first report of a positive culture, rather than to wait for sensitivity tests. For this reason, with the staphylococci we used very large doses of penicillin intravenously (5,000,000 to 30,000,000 units daily) and streptomycin intramuscularly. When the sensitivity tests became available, other antibiotics were added if there had been no clinical response.

At present only 8 of the 20 patients are alive. One of those dead recovered from his infection, but died of congestive heart failure 18 months later (case 7). One apparently recovered, but died of a relapse 6 months later, during surgery for a mycotic femoral aneurysm, the aneurysm probably resulting from an infected embolus (case 3). Another died of undetermined cause 6 months after completing therapy of her infection (case 19). In 1 case the patient had been afebrile for 48 hours, and died of heart failure, with evidence over some days of an increasingly dynamic aortic regurgitation (case 5). Finally, 2 cases can hardly be said to have been treated, since the diagnosis was not made until the last few days of life (cases 12 and 18), 1 case having been mistaken for rheumatic fever (case 18). Six cases remain in which presumably adequate therapy was truly a failure, 8 in which it was successful.

SUMMARY

Twenty cases of bacterial endocarditis occurring after cardiac surgery, in a total of

2,263 cases operated between 1950 and 1955, are reviewed. There was 1 instance among 374 cases of congenital heart disease, 19 among 1,889 cases with acquired valvular heart disease. Aortic valvular disease predominated among the cases of rheumatic heart disease (10 out of 19); mitral disease was the background in 6 cases; combined aortic and mitral disease in 3. Among the 19, fairly heavy valvular calcification was present in 11.

Aortic commissurotomy was the most frequently performed operation. In 4 cases a nylon foreign-body was introduced above the aortic valve to try to correct aortic insufficiency. Eight cases had a mitral commissurotomy, but 3 of these were in association with aortic surgery.

About one third of the cases occurred early (within 10 days after surgery), one-third late (more than 3 months after surgery), and the remaining one-third were in the intermediate group. The most common infecting organism (14 cases) was the staphylococcus, the coagulase-negative variety far more frequently than any other. These organisms were generally quite resistant to penicillin, both in the bacteriologic laboratory and clinically. With a variety of therapy, which was generally fairly massive, 8 patients are living and well. Of the 12 dead, 6 must be considered true failures of treatment of the infection.

Clinically and bacteriologically, bacterial endocarditis occurring after cardiac surgery seems to be a more malignant lesion than the common subacute variety seen in nonsurgical cases. This increased severity is probably a reflection of the trauma to the valve, the nature of the organism causing the infection, and the severe stress to which the patient has been subjected.

SUMMARY IN INTERLINGUA

Es presentate un revista del 20 casos de endocarditis bacterial occurrente postchirurgicamente in un total de 2.263 operationes cardiac executate inter 1950 e 1955. Un del 20 casos representava un gruppo de 374 operationes in casos de congenite morbo cardiac; le altere 19 representava le 1.889 casos de acquirite morbo de valvula cardiac. Morbo del valvula aortic predominava inter le casos

de rheumatic morbo cardiac (10 ex 19). Morbo mitral eseva al fundo de 6 casos. Le combination de morbo mitral e aortic characterisava 11 casos. Inter le 19 casos de rheumatic morbo cardiac, 11 revelava le presentia de satis sever grados de calcification valvular.

Commissurotomy aortic eseva le operation executate le plus frequentemente. In 4 casos un corpore alien de nylon eseva introduce supra le valvula aortic in le effortio de corrigir le insufficientia aortic. Commissurotomy mitral eseva le operation in 8 casos, sed in 3 de illos le commissurotomy mitral eseva associate con chirurgia aortic.

Circa un tertio del casos occurreva promptemente (intra 10 dies post le operation); un tertio tardivamente (plus que 3 menses post le operation); e le ultime tertio constitueva un gruppo intermediari. Le plus commun organismo infective eseva le staphylococcus (14 casos). Le varietate coagulase-negative eseva plus frequente que omne le altere varietates. Iste organismos se monstrava generalmente satis resistente a penicillina, tanto in le laboratorio bacteriologic como etiam clinicamente. Un varietate de therapias de character generalmente massive eseva usate. Octo del patientes vive e se trova ben. Ex le total de 12 mortes, 6 debe esser considerate como clarmente causate per non-successo del tractamento del infection.

Ab le punctos de vista clinic e bacteriologic, endocarditis bacterial post chirurgia cardiac es apparentemente un lesion plus maligne que le subacute varietate commun que es incontrate in casos nonchirurgic. Iste plus alte grado de severitate es probabilemente un reflexion del trauma valvular, del natura del organismo que causa le infection, e del severitate del stress que le patiente ha absorbite.

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"Left Heart" Radiopotassium Dilution Curves in Patients with Rheumatic Mitral Valvular Disease

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"Left heart" radiopotassium-dilution curves were carried out in 9 patients with rheumatic mitral valvular disease. From the curves, blood flow, circulation times, and "left heart" and aortic volumes were calculated. When this technic is used along with "left heart" pressure measurements, it appears to have a satisfactory reliability in demonstrating abnormalities of flow, volume, and mitral valve function. In theory, its proper application permits complete quantitation of these parameters.

IN SOME patients having long standing rheumatic heart disease routine clinical studies are inadequate either in establishing the existence or in evaluating the severity of stenosis or insufficiency of the mitral valve. Yet corrective surgical treatment makes evaluation of mitral valve function a matter of considerable importance. The surgical procedure, the surgical mortality, and the prognosis covering postoperative improvement are all influenced to some extent by the nature of the lesion present.

A number of specialized diagnostic procedures have been employed to improve diagnosis and quantify approximately the degree of the abnormalities present. Among these are angiocardiology,¹ measurement of pulmonary arterial "wedge" pressure,² ballistocardiography,³ and direct measurement of "left heart" pressure.⁴ Yet, mistaken evaluations are still occasionally made or corroborative evidence is desired, particularly with respect to the amount of insufficiency present. It was considered that indicator-dilution curves made by injections of an indicator into the left heart and aortic root could be used to provide additional and perhaps better information on blood flow, valve function, and also on left heart volume.

The data so far available from radiopotassium-dilution curves in 9 patients with valvular

disease limited to the mitral valve have led us to hope that this technic, with the addition of left atrial sampling technics as recently advocated by Wood's group,⁵ and combined with presently used left heart pressure measurements, will permit a rather complete and quantitative description of mitral valve orifice area (both in systole and diastole), and of the pressure-volume-blood flow relationships in the left side of the heart.

METHOD

Patients with known or suspected rheumatic valvular heart disease, candidates for corrective surgical measures, were studied. Nine had valvular disease limited to the mitral valve, and they are included in this report. Only patient 9 had any appreciable signs or symptoms of myocardial failure.

Small plastic catheters were inserted into the left atrium and ventricle⁶, and an indwelling Cournand needle was introduced into the femoral or brachial artery. A small plastic catheter was passed in retrograde fashion under fluoroscopic guidance from the other femoral artery until its tip lay in the root of the aorta. After pressure measurements had been recorded in the various chambers, radiopotassium-dilution curves were made. Consecutive injections of 15 to 20 μ c. of radiopotassium (K^{42}) in a volume of about 0.2 ml. were made into the left atrium, left ventricle, and root of the aorta. Femoral arterial blood was then sampled and its radioactivity counted with respect to time for the next 30 to 60 seconds. For this purpose the blood was drawn by a mercury gravity vacuum pump at the rate of approximately 0.5 ml./sec., through a cuvette (0.3 ml. volume) contained within a well-type scintillation counter. The dead space from blood vessel to cuvette was about 0.8 ml. The scintillation counter was linked to a specially built logarithmic counting rate

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meter,* which in turn fed the counts to a Brown Recorder (0.5 second full scale response) on which the log of concentration was recorded with respect to time.

Calculations

Cardiac output was calculated from the curves according to the Hamilton method. The cardiac index was then determined using standard height-weight body surface tables. The mean circulation time from injection to sampling site was measured as described by Hetzel,⁷ and the total volume of blood between the sites calculated as mean circulation time times cardiac output.

For purposes of evaluating chamber mixing volumes the part of the circulatory system under study was considered as a system consisting of 3 compartments, left atrium, left ventricle, and aorta, that are connected in series and have no back flow or feed back. The ventricular and at least part of the aortic blood were considered under normal circumstances to undergo complete mixing within 1 cardiac cycle, with exponential washout of indicator in a discontinuous fashion from the ventricle, and in a continuous fashion (obviously an approximation) from the aorta. In practice, the nature of the blood sampling imparted the general appearance of a continuous curve to all parts of the experimental curves. Atrial blood was considered to undergo essentially no mixing except in the case of insufficiency wherein there is a third mixing compartment in the system and regurgitant flow from ventricle to atrium. Unfortunately it was not initially appreciated that with mitral insufficiency a more complicated model system analysis was indicated and that our experimental data were insufficient to permit complete characterization of flow-volume parameters in the more complicated system. The addition of a left atrial sampling curve following left ventricular injection, if representative, would have allowed a complete analysis. In the absence of this information and in the presence of mitral insufficiency the data of left heart residual volume must be thought of as indicating the approximate sum of left atrial and ventricular mixing volumes minus stroke volume, and the amount of mitral regurgitation can be evaluated only indirectly.

Other assumptions and requirements tacitly accepted by users of the indicator-dilution principle have been enumerated and discussed by Newman and associates⁸ and by Meier and Zierler.⁹ Mathematical analysis of the model system used here, following the exponential washout equations developed by Newman,⁸ leads to the results that the concentration (P_2) of indicator at any time, as sampled in the femoral artery subsequent to left atrial or ventricular injection, has the following relationships:

$$P_2 = \frac{P_0}{k_2 + \ln \left(\frac{V_R}{V_R + V_E} \right)^{\frac{F}{V_E}}} \left[\left(\frac{V_R}{V_R + V_E} \right)^{\frac{F}{V_E} t} - e^{-k_2 t} \right] \quad (1)$$

where k_1 and k_2 are exponential washout rate constants from left heart and aorta respectively; V_R = residual volume (left heart); V_E = stroke volume; F = cardiac output.

The time-concentration curve is thus composed of 2 exponential terms whose rate constants (k_1 and k_2) have the relationships

$$k_1 = \frac{F}{V_E} \ln \frac{V_R}{V_R + V_E} \quad (2)$$

and

$$k_2 = \frac{F}{V} \text{ (aortic)}. \quad (3)$$

The appropriate rate constants (k 's) are determined by graphic analysis of the experimental curves. The k_2 representing the aortic washout is obtained from injection in the root of the aorta as well, so as to show which of the 2 k 's obtained from left heart injection curves represents left heart washout. For the aortic injections the concentration relationships with time are

$$P_2 = P_0 e^{-k_2 t} \quad (4)$$

and the relationship of k_2 to flow and volume the same as in equation (3). With blood flow already known from the dilution curves, and heart rate obtained, left heart mixing volumes and aortic mixing volumes were calculated.

Evaluation of Patients

An independent estimation of the amount of mitral stenosis and of the amount of mitral insufficiency was made in order to evaluate the radiopotassium-dilution curve as a measure of valve function. The independent estimation was based on information gathered by history and physical examination, fluoroscopy (9 patients), angiocardiology (6 patients), wedge-pressure measurements (4 patients), left heart pressure measurements (9 patients), surgical exploration (4 patients), postmortem examination (1 patient), and ballistocardiography. It was fully realized that the only true test of our technics would be their demonstration of the correct diagnosis in patients in which all other tests were in disagreement, inaccurate, or not informative. This demonstration would require in turn an infallible index of reference, an index that may not be found even in the surgeon's palpating finger or in a postmortem examination. The nearest substitute for an ideal standard of ref-

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erence seemed to be the grading of patients into categories of 0 to 4 degrees of mitral stenosis or insufficiency on the basis of the sum of the above studies with emphasis particularly on the findings at operation and necropsy.

RESULTS

All the results except the aortic mixing volumes are shown in table 1. The diagnoses determined by other studies are shown in column 1 of that table. The general shape of the curves obtained from left heart injections is shown in figure 1. The contour of the curve in the patient with mitral stenosis was similar to normal but the terminal slope was frequently modestly flattened ($k = 0.15$ to 0.25 per second) whereas with mitral insufficiency the

terminal slope was definitely abnormal, being very much flatter, or less steep, than normal ($k = .03$ to $.07$ per second).

Cardiac Output and Stroke Volume

In all 9 patients the cardiac output was subnormal, averaging $2.1 \text{ L./M.}^2/\text{min.}$, and ranging from a high of 2.6 to a low of 0.9 in patient 9 with "pure" mitral stenosis and cardiac failure. Most of these patients had atrial fibrillation so that only an average stroke volume could be determined. It was decreased in all patients in much the same manner as was cardiac output, ranging from 18 to 66 ml. and averaging 40 ml. per beat.

TABLE 1.—Hemodynamic Results

Patient no. and diagnosis*	Indicator injection site	Cardiac index (L./M. ² /min.)	Mean stroke volume† (ml.)	Onset of curve (sec.)	Peak of curve (sec.)	Mean circulation time (sec.)	Left heart mixing volume (V _R) (ml.)	Total volume, inj. to sample site (V _T) (ml.)	$\frac{V_R}{V_T}$
1	L. At.	2.3	41	5.0	9.5	16.5	890	1020	0.88
MI 4	L. V.	2.3	41	5.0	9.5	16.0	880	1000	0.88
2	L. At.	2.2	45	8.0	13.0	22.0	1000	1530	0.65
MI 4	L. V.	2.2	45	8.0	13.0	19.0	830	1300	0.64
3	L. At.	2.1	38	7.0	12.0	21.5	1300	1200	1.08
MI 4	L. V.	2.3	41	6.0	11.0	20.5	1400	1200	1.17
4	L. At.	2.1	39	10.0	15.0	26.0	1200	1520	0.79
MI 3 MS 0-1	L. V.	2.1	39	8.0	12.5	23.0	1040	1340	0.78
5	L. At.	2.1	28	9.5	19.0	19.5	440	940	0.47
MI 2 MS 1	L. V.	2.1	28	8.5	17.0	18.5	530	870	0.61
6	L. At.	1.8	40	2.5	5.0	8.5	300	460	0.65
MI 2 MS 2	L. V.	1.9	41	2.0	4.0	6.0	250	330	0.75
7	L. At.	2.3	45	5.0	9.5	11.5	355	690	0.52
MI 2-3 MS 1	L. V.								
8	L. At.	2.6	66	7.0	15.5	17.0	590	1420	0.42
MI 2 MS 2	L. V.	2.5	62	5.0	13.0	15.0	480	1250	0.38
9	L. At.	1.0	18	16.0	22.0	24.0	90	720	0.13
MS 4 Failure	L. V.	0.9	18	5.0	8.0	10.0	90	300	0.30
Normal Values		2.7-3.5	50-90	3-5	5-7	5-8	60-80	300-600	LA 0.15-0.20 LV 0.20-0.25

* See text for diagnostic evaluation methods; MS = mitral stenosis, MI = mitral insufficiency.

† Most of the patients had atrial fibrillation.

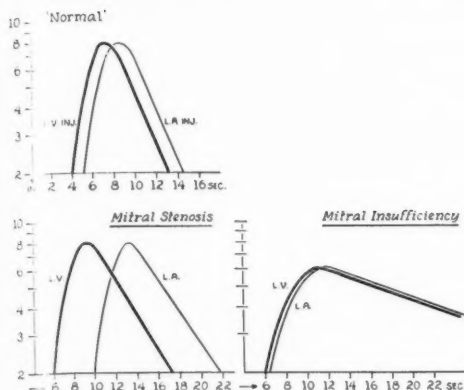


FIG. 1. Radiopotassium-dilution curves obtained from left atrial (thin line) and left ventricular (thick line) injections. Ordinate, concentration (counting rate) plotted logarithmically; abscissa, time in seconds. The curves in mitral stenosis differ from the normal curves in a somewhat decreased terminal slope and a significant delay in the onset of activity time (10 seconds) of the left atrial curve over (6 seconds) the left ventricular curve. The curves in mitral insufficiency differ from the other curves in the markedly flattened terminal slope, the reduced peak concentration, and the almost identical time-concentration relationships.

Circulation Times

In patients 1 to 4 with essentially pure mitral insufficiency the onset of activity time (beginning of dilution curve) was normal or only slightly delayed, whereas the peak of activity was considerably delayed and mean circulation time prolonged up to 3 times normal. These circulation times in these patients were nearly alike, irrespective of whether the left atrium or left ventricle was the site of injection for indicator, the "left ventricular" times being about 90 to 100 per cent of the "left atrial" times. In patients 5 to 8 having mixed stenosis and insufficiency the same general pattern was seen with regard to the circulation times except that the mean circulation times in general were more nearly normal, and in each patient, all the atrial and ventricular circulation times showed a consistent difference. The "ventricular" times were consistently shorter than the "atrial," averaging about 85 per cent of the latter times. In the 1 patient with essen-

tially "pure" mitral stenosis and cardiac failure this tendency was greatly exaggerated. All atrial injection circulation times in this patient were appreciably prolonged, whereas those from the ventricular injection were only slightly prolonged. Thus there was a considerable time differential, the ventricular times averaging about 35 per cent of the atrial times.

Volumes

The total volume of blood between the left atrial injection site and the femoral arterial sampling site was increased in all except patient 6. The increases were most marked in the patients presumed to have the most insufficiency, averaging 1.37 L. in patients 1 to 4. As would be expected from the circulation times, the total blood volume from left ventricular injection site to femoral artery sampling site was also increased appreciably to 1.21 L. in patients with insufficiency. The 2 volumes approximated each other in each of these patients. Total volume increases in the other patients with less insufficiency and more stenosis were generally less marked, total volume in these averaging only 0.85 L. with left atrial injections and only 0.78 L. with left ventricular injections. In the patient with stenosis alone, only the indicated volume of blood between atrium and femoral artery was moderately increased, whereas volume between ventricle and artery was within normal limits. This would be expected with left atrial enlargement alone. The left heart mixing volume (the residual left heart volume after subtraction of ejection volume) was increased in all patients with the exception of patient 9 with pure stenosis. The increases resulted in volumes up to about 1.5 L., or values nearly 20 times normal. The increases correlated reasonably well with the amount of mitral insufficiency as estimated by other procedures and correlated inversely nearly as well with the amount of stenosis (table 1). The ratio of mixing to total volumes $\frac{V_R}{V_T}$ correlated even better with the functional abnormality. High ratios, averaging 0.85, were found with "pure" mitral insufficiency; lower ratios, averaging 0.53, were found

with mixed lesions; and an essentially normal or even subnormal ratio was found with "pure" stenosis and cardiac failure.

The aortic mixing volumes ranged from 100 to 160 ml. in the women and 150 to 220 ml. in the men. Total blood volume from root of aorta to femoral artery averaged 310 ml. and ranged from 250 to 350 ml.

DISCUSSION

These left heart indicator-dilution curves and their analysis provide evidence bearing on the following matters:

Diagnosis of Functional State of Mitral Valve. The contour of the curves obtained from left heart injection in subjects with mitral insufficiency can be easily differentiated from the curves associated with mitral stenosis (fig. 1). The former has a longer ascending limb, a lower peak concentration, and a much flatter terminal exponential slope than do the latter or do normal curves. The curves in "mitral stenosis" differ very little from normal curves we have obtained in dogs. The only consistent difference is a slightly flatter than normal terminal slope, which is presumably due to the subnormal cardiac output, since subjects with normal mitral valves and low cardiac output also have curves with a similar flattening of slope, as would be predicted by the "washout" theory of Newman.⁸ Thus, differentiation of a normal valve from a stenotic valve on the basis of curve contour alone does not appear feasible, while the presence of insufficiency can be diagnosed merely by casual inspection of the contour of the dilution curve unless blood flow is exceptionally low. In this case quantitation must be employed.

Stroke Volume and Cardiac Output in Rheumatic Mitral Valvular Disease. As has been generally recognized in patients with longstanding, marked rheumatic mitral valvular disease, cardiac output and stroke volume are consistently and definitely subnormal; about $\frac{2}{3}$ normal, when the subjects are at rest.

Left Heart Volumes in Mitral Rheumatic Heart Disease. Also as generally appreciated, left heart total blood volumes (volume of left atrium to femoral artery minus volume of

root of aorta to femoral artery) are consistently increased in all patients with mitral disease. In general the largest increases were associated with the most mitral insufficiency. Left heart volumes as high as 1.2 L. were recorded in our patients with marked insufficiency by means of the calculation of the mean circulation time times cardiac output. With regard to the calculated mixing volumes, the curves are not sufficient for making a separate evaluation of ventricular residual mixing (presumably total ventricular residual) volume and of atrial mixing volume when turbulence is occurring in both chambers as in the patient with regurgitation. However, when a maximum value of 300 to 400 ml., well above the normal value of 80 to 90 ml., was assigned to ventricular residual volume, we not only found this increase in ventricular volume but also a large atrial mixing volume attributable to a strong regurgitant jet that would produce atrial turbulence. In fact, this calculation indicated atrial mixing volumes as high as 1.0 L. associated with grade 4 insufficiency in patient 3. This mixing volume is approximately equal to, and in one case greater than, the calculated total atrial volume. Stated otherwise, the high ratios of mixing to total blood volume, averaging near unity in the combined left heart and aortic segments of patients with marked insufficiency indicate that nearly the entire blood flow in the left heart is turbulent. Indeed these ratios, along with the nearly identical, prolonged circulation times resulting from atrial and ventricular K^{42} injections, suggest that, as far as filling and mixing are concerned, patients with "pure" insufficiency have a functionally single left heart chamber composed of an enlarged left atrium and ventricle that are not separated at any time in the cardiac cycle.

With increasing mitral stenosis and decreasing insufficiency, total and mixing volumes were still elevated, though less markedly so, and the figures of 400 to 600 ml. for mixing volume are in agreement with both a moderate increase in ventricular residual volume and an appreciable atrial mixing volume. However, that the increased atrial volume was not entirely

involved in turbulent mixing, and that the regurgitant jet effect was decreased (compared to "pure" insufficiency) was indicated by the intermediate, only moderately elevated mixing to total volume ratios of 0.40 to 0.80.

In patient 9, the only one with "pure" stenosis, the only abnormality in volume was an increased left atrial volume to about 400 ml. The calculated left heart residual volume (mixing volume) was almost normal, compatible with an essentially normal left ventricular size and mixing and no atrial mixing (volume); thus a regurgitant flow was excluded indirectly. These data are consistent with the view that in "pure" stenosis the only appreciable derangement in left heart volume is an increased atrial volume in which there is no turbulence of flow. It seems prudent to point out, however, that these views are based on the findings in 1 patient, who had a very low cardiac output. Evidence of appreciable mixing in the atrium may be discovered under conditions of more normal blood flow.

Left Heart Circulation Times in Rheumatic Mitral Valve Disease. The prolonged, nearly identical circulation times from left ventricle to artery and left atrium to artery in mitral insufficiency are also in line with the concept that indicator is washed back and forth between 2 enlarged heart chambers, which, except for their out-of-phase activities, could be functionally considered as a unit. The differential in these times with stenosis and the apparent increased differential with increasing stenosis is in line with the concept of delay of indicator, whatever its explanation, on the atrial side of the stenotic valve.¹

Quantitative Diagnosis of Left Chamber Volumes, Forward and Regurgitant Flow, and Valve Orifice Areas. The present analytic method and experimental curves are, as far as we know, adequate to describe the above parameters in subjects with no mitral regurgitant flow, in whom simultaneous pressures are recorded. Thus, it appears "pure" mitral stenosis can be recognized and the degree partially quantified by the difference in circulation times from atrium and ventricle to artery and by the subnormal ventricular residual to total left

heart volume ratio as well as by calculation with Gorlin's formulas.^{10, 11} These parameters are not all properly quantitated in the presence of insufficiency. However, the presently observed good correlations, particularly of the "equalization" and prolongation of left heart mean circulation times and the high ratios of left heart mixing volume to total volume, with the degree of insufficiency diagnosed by other procedures, convince us that we can determine the left atrial mixing volume for practical purposes and thus, indirectly, the amount of insufficiency present. The differentiation of the case with insufficiency with no stenosis from insufficiency with some stenosis does not seem on very firm grounds except from inference based on the knowledge that in rheumatic disease the 2 lesions usually coexist when 1 is of moderate degree.

It is likely, however, that the present inadequacies are based more on the experimental design used than on the methods employed. If a curve from another sampling site is obtained, the entire model system can be characterized with regard to forward and backward flow and chamber volumes. As stated previously, Wood's group⁵ has been aware of this problem also and have started drawing left atrial samples following left ventricular injections of indicator. If the blood sample can be shown to be truly representative of mixed atrial blood and the model analysis is essentially valid, the indicator-dilution curves will permit evaluation of all flows and volumes and the simultaneously obtained pressure curves along with Gorlin's formulas^{7, 8} will permit an estimation of the functional area of the mitral valve during both systole and diastole. Conversely, if the surgeon can accurately determine orifice area, measurements of indicator-dilution flows and appropriate left heart pressures can be used conjointly to provide an in vivo test of the mitral valve formulas.

SUMMARY

Nine patients having long standing rheumatic valvular heart disease involving only the mitral valve were studied by a left heart radio-potassium-dilution curve technic during left

heart catheterization. Arterial dilution curves were obtained following left atrial, left ventricular, and aortic root injections.

Results showed (a) gross differences between the left heart injection curves in mitral stenosis and those in insufficiency; (b) low cardiac output and stroke volume in all patients; (c) left heart mixing and total volume changes, the ratios of which were high with mitral insufficiency and normal or low with stenosis; (d) variations in circulation times from left atrial and ventricular injections, with similar times in mitral insufficiency, appreciably different times in mitral stenosis, and intermediate values with combined lesions.

The results are consistent with the concept that in mitral stenosis the only important change in volume or blood flow in the left heart is an increased total atrial volume, whereas in mitral insufficiency not only are both atrial and ventricular total volumes increased but also turbulence of flow then occurs, because of the regurgitant jet, in most or all of the atrium, in addition to the ventricle.

Evaluation, by the dilution curves, of mitral valve dysfunction and amount of regurgitant blood flow, although apparently quite satisfactory, is indirect. With the use of an appropriate additional curve and simultaneously measured left heart pressures, it is possible, in all patients, to calculate the volumes of the separate chambers, the volume of regurgitant flow, and the area of the mitral valve orifice, both during systole and diastole.

SUMMARY IN INTERLINGUA

Esseva studiate 9 patientes con prolongate rheumatic morbo cardiovalvular, afficiente solmente le valvula mitral. Le studio esseva executate per medio de un technica a curvas de dilution de radiokalium in le corde sinistre durante catheterisation sinistro-cardiac. Curvas de dilution arterial esseva obtenite post injectiones in le atrio sinistre, le ventriculo sinistre, e le radice aortic.

Le resultatos indicava (a) grande differentias inter le curvas de injection sinistro-cardiac in stenosis mitral e in insuffientia mitral; (b) basse valores pro le rendimento cardiac e le

volumine per pulso in omne patientes; (c) alterationes de mixtion sinistro-cardiac e de volumine total con proportionones que esseva alte in insufficientia mitral e normal o basse in stenosis; (d) variationes del tempores circulatori post injectiones sinistro-atrial e sinistro-ventricular, con simile tempores in casos de insufficientia mitral, satis differente tempores in stenosis mitral, e valores intermediari in casos de lesiones combinate.

Le resultatos es de accordo con le concepto que in stenosis mitral le sol importante alteration de volumine o de fluxu sanguinee in le corde sinistre es un augmento del total volumine atrial, durante que in insufficientia mitral il ha non solmente un augmento del volumines total tanto atrial como etiam ventricular sed in plus un occurrentia de fluxu turbulente que se manifesta, a causa del regurgitation explosive, in le plus grande parte del atrio o mesmo in le atrio integre e non solmente in le ventriculo.

Le evaluation, per medio de curvas de dilution, de dysfunction del valvula mitral e del quantitate del regurgitante fluxu sanguinee es certo satis adequate, sed illo es nonobstante indirecte. Per usar un appropriate curva additional e per mesurar simultaneamente le pression sinistro-cardiac, il es possibile calcular le volumine del cameras individual in omne patientes e etiam le volumine del fluxu regurgitante e le area del orificio del valvula mitral, tanto durante le systole como etiam durante le diastole.

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Cheyne-Stokes Respiration. But there is a symptom which appears to belong to a weakened state of the heart, and which, therefore, may be looked for in many cases of the fatty degeneration. I have never seen it except in examples of that disease. The symptom in question was observed by Dr. Cheyne, although he did not connect it with the special lesion of the heart. It consists in the occurrence of a series of inspirations, increasing to a maximum, and then declining in force and length, until a state of apparent apnoea is established. In this condition the patient may remain for such a length of time as to make his attendants believe that he is dead, when a low inspiration, followed by one more decided, marks the commencement of a new ascending and then descending series of inspirations. This symptom, as occurring in its highest degree, I have only seen during a few weeks previous to the death of the patient. I do not know any more remarkable or characteristic phenomena than those presented in this condition, whether we view the long-continued cessation of breathing, yet without any suffering on the part of the patient, or the maximum point of the series of inspirations, when the head is thrown back, the shoulders raised, and every muscle of inspiration thrown into the most violent action; yet all this without rale or any sign of mechanical obstruction. The vesicular murmur becomes gradually louder, and at the height of the paroxysm is intensely puerile.

The decline in the length and force of the respirations is as regular and remarkable as their progressive increase. The inspirations become each one less deep than the preceding, until they are all but imperceptible, and then the state of apparent apnoea occurs. This is at last broken by the faintest possible inspiration; the next effort is a little stronger, until, so to speak, the paroxysm of breathing is at its height, again to subside by a descending scale.—WILLIAM STOKES. *The Diseases of the Heart and the Aorta*. Dublin, 1854.

Healed Dissecting Aneurysm in Cystic Medial Necrosis of the Aorta

By PETER B. HUKILL, M.D., CAPT. USAF (MC)

Dissecting aneurysm of the aorta is a not uncommon disease that usually produces severe symptoms and often leads to an early death. This article reports an unusual case in which the patient was nearly asymptomatic and died of unrelated causes. Autopsy revealed a healed dissecting aneurysm. The literature on dissecting aneurysm, emphasizing its pathogenesis and its relation to cystic medial necrosis, is briefly reviewed.

DISSECTING aneurysm of the aorta has long been recognized as a disease entity, and is ordinarily regarded as a rapidly fatal condition. A certain proportion of dissecting aneurysms redissect into the lumen of the aorta, forming the so-called "double-barreled" aorta. Occasional cases of dissecting aneurysm have survived for a considerable period after the acute episode, many of them being of the "double-barreled" variety.¹⁻⁷ Most of the reported prolonged survivals suffered from congestive heart failure and eventually died as a result of the aneurysm.^{2, 4, 7} Few cases have been reported in which the dissecting aneurysm was essentially an incidental autopsy finding of relative clinical insignificance.⁸ The following case report is presented as an instance of chronic, nondisabling dissecting aneurysm associated with idiopathic cystic medial necrosis.

CASE REPORT

Clinical Findings

The patient was a 43-year-old white male military officer. In 1950, a malignant melanoma was removed from his left shoulder. He had no further difficulties until he suffered transient episodes of vertigo and blurring of vision in February and June 1953. A physician at that time found no cause for the vertigo. In March 1954 a cardiac murmur was first noted. In August 1954 2 more episodes of vertigo were followed by syncope. At this time examination showed atrial fibrillation and the patient was hospitalized. The rhythm reverted to normal after digitalization and the patient returned to duty. Fibrillation recurred in October 1954 and was again controlled with digitalis. He was hospitalized on September 5, 1955, for study of his cardiac condition.

From the Histopathology Center, 3275th USAF Hospital, Parks Air Force Base, Calif.

The patient denied any history suggesting acute rheumatic fever. He had been in the military service continuously since the age of 20 and had enjoyed good health. He had no history of chest pain, dyspnea, or palpitation. The patient underwent a tonsillectomy in childhood and an appendectomy at the age of 21. At the time of the appendectomy physical examination of the heart was normal; blood pressure was recorded at 138/58. Subsequent determinations, however, revealed a normal pulse pressure. In the family history, the patient's mother had died of heart disease at 59.

On admission to another Air Force hospital in September 1955, the blood pressure was 124/40. Grade III systolic and diastolic murmurs were heard over the aortic area, radiating to the neck, and the peripheral signs of aortic insufficiency were present. Chest x-ray showed minimal cardiac enlargement and widening and tortuosity of the aorta. An electrocardiogram showed normal sinus rhythm, left ventricular hypertrophy, and digitalis effect. Routine blood counts and urinalyses were normal. Serologic test for syphilis was negative. The basal metabolic rate was plus 1, and an electroencephalogram was normal. Shortly after admission a complete neurologic examination revealed a left pupil slightly larger than the right. The patient's syncopal attacks were attributed to his heart disease, which was thought most probably to be rheumatic in origin.

While in the hospital the patient began complaining of headaches and of flashing lights in his field of vision. Over a period of a few days he became markedly lethargic. On October 22 papilledema was noted, as well as asymmetrical reflexes in the lower extremities, and a right Babinski sign. A ventriculogram showed a space-occupying lesion in the right cerebral hemisphere. On craniotomy a walnut-sized tumor was found under the right premotor cortex and it was enucleated. Pathologic diagnosis was metastatic tumor, probably malignant melanoma. The patient made a good recovery from the operation, complicated only by recurrent infection of the urinary tract. During hospitalization the blood pressure averaged 130/40.

On December 2 the patient was transferred to Parks Air Force Base Hospital. Admission blood

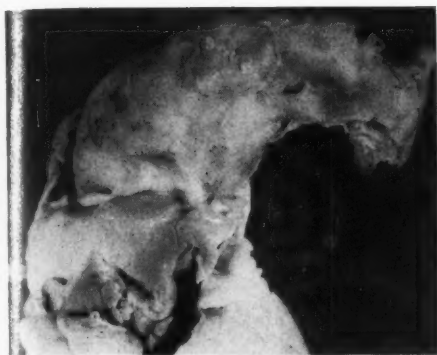


FIG. 1. External view of the aortic arch, showing the aneurysmal dilatation of the ascending portion.

pressure was 120/40. The patient was oriented and alert, and showed a left hemiparesis. Cardiac findings were as previously described. Fine rales were noted at the left base posteriorly. Routine laboratory studies were negative except for evidence of a urinary tract infection. Chest x-ray showed for the first time a solitary, circumscribed lesion in the right lower lung field. The heart was minimally enlarged. An electrocardiogram showed atrial fibrillation and digitalis effect. Over a period of about 2 months the patient's neurologic status gradually improved on a regimen of physiotherapy, and he began to walk. He had no complaints referable to the cardiovascular system. Late in February, however, his general condition began to deteriorate. A new pulmonary lesion was noted, and hard nodes appeared in the neck. He died on February 23, following a generalized seizure.

Autopsy Findings

Evidence of the healed craniotomy was noted. Variably pigmented nodules of metastatic tumor were found widely scattered in the endocardium, epicardium, lungs, liver, adrenal glands, mediastinal, retroperitoneal, and cervical lymph nodes, and in the brain and meninges. The other notable findings were limited to the cardiovascular system.

The heart weighed 450 Gm. and was not dilated. It showed minimal hypertrophy of the left ventricle. The aortic valve ring measured 7.5 cm. in circumference. The cusps were not separated and had their usual thin, membranous appearance. The valve did not appear to be anatomically stenotic or incompetent. The ascending portion and arch of the aorta were involved in a fusiform dilatation (fig. 1). The adventitial surface of the aorta was smooth and not involved in adhesions or fibrosis. The caliber of the aorta increased rapidly above the valve, reaching its maximum of 8.5 cm. diameter about 4 cm. above it. The ascending aorta and arch had a double lumen beginning 8 cm. above the aortic valve and ending

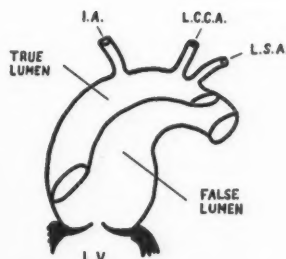


FIG. 2. Diagram showing extent and relations of dissection, which is larger than, and lies inferior to, the original lumen.



FIG. 3. View of the aortic arch opened via the secondary channel, showing the intact original channel (arrows), which gives origin to the innominate, left common carotid, and subclavian arteries.

1 cm. distal to the origin of the left subclavian artery (fig. 2). The proximal intimal tear, which measured 3.5 cm. in length, lay at about 45 degrees to the axis of the aorta. The 2 lumens were separated by a leathery septum approximately 2 mm. in thickness, both of whose surfaces were smooth and shiny (fig. 3). The smaller lumen, which measured 6.5 cm. in circumference at its origin and 4.0 cm. at its termination, lay superior and somewhat posterior to the larger lumen and gave origin to the innominate, the left common carotid, and the left subclavian



FIG. 4. Photomicrograph of media in area near dissection showing zone of muscular necrosis and adjacent early cystic change. (Hematoxylin and eosin, $\times 100$.)

arteries. The septum underlying the origin of these arteries was intact. The intima of the aorta in the dilated portion showed slight longitudinal wrinkling and only an occasional slightly elevated plaque, as did the thoracic and abdominal aorta. There was no calcification, ulceration, or thrombosis. There were no congenital anomalies of the heart, and the remainder of the autopsy was essentially unremarkable.

Microscopic examination of the tumor masses showed an anaplastic tissue with dense focal pigmentation typical of malignant melanoma.

Microscopic sections from various portions of the aorta showed conspicuous changes in the media. Several sections showed long zones of muscular "necrosis" where the muscle fibers retained their outlines but had lost their nuclei and stained more deeply with eosin than the surrounding tissue (fig. 4). These necrotic bands varied in width up to one third of the thickness of the media and extended longitudinally for several centimeters. There were numerous, scattered, sharply delineated areas of myxomatous change in which no muscular or fibrous tissue was seen, but which consisted of fusiform or stellate cells irregularly arranged in a mucoid ground substance. These areas bore no notable relation to the zones of muscular degeneration and abruptly interrupted the regular architecture of the surrounding media, which showed no evidence of cellular infiltration or vascular proliferation. Some of these lesions had progressed to the point of cyst formation (fig. 5) and contained completely acellular mucoid material. An occasional cystic lesion showed

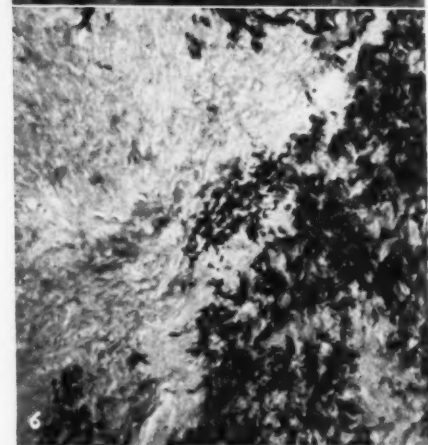


FIG. 5. Photomicrograph of section of the aorta adjacent to the dissection, showing cystic change in the media. (Hematoxylin and eosin, $\times 100$.)

FIG. 6. Photomicrograph of section of the aneurysmal wall, showing fragmentation and disorganization of elastic fibers and their complete absence in cystic area. (Verhoff-van Gieson, $\times 100$.)

evidence of organization with fibroblastic invasion, but this change was infrequent.

Sections stained with Verhoff's elastic stain showed large areas in which the elastic fibers were markedly thickened and fragmented and had lost their usual orderly arrangement (fig. 6). The areas of disruption of elastic tissue were always closely associated with the cystic lesions. The cystic lesions themselves were invariably completely devoid of elastic fibers. Sections from septum between the true and false channels showed it to be composed of a lamina of medial tissue of about half the normal thickness, covered on one side by an essentially

normal intima and on the other by much thinner condensation of fusiform cells, which in turn was lined by endothelium. The medial tissue of the septum showed relatively little necrosis and cyst formation. Similarly, sections from the wall of the dissection showed it to be composed of a thinner-than-normal media lined by a very thin intima-like tissue.

The various sections showed focal intimal changes suggesting only an early stage of atherosclerosis. The intima was focally thickened and contained small accumulations of foam cells and showed slight fibroblastic proliferation.

DISCUSSION

Cases of dissecting aneurysm have been recognized since the sixteenth century. Early descriptions of the disease were given by Vesalius⁹ and by Nichols.¹⁰ Rokitsky,¹¹ in 1852, gave an accurate general description of the anatomic changes and a perceptive discussion of the pathogenesis. His views were remarkably modern, and he attributed dissecting aneurysm to a primary disease of the media, rather than to an intimal defect, expressing an attitude that is only recently becoming generally accepted. Rokitsky's conclusions are all the more astute for being based almost entirely on gross observations.

Most early reports of dissecting aneurysm dealt with patients of relatively advanced age; many authors, despite Rokitsky's early views to the contrary, regarded the condition as a disease of old age and associated it with senescence, arteriosclerosis, and hypertension.⁸ As recently as 1953, Jackson and Slavin¹² suggest that a combination of arteriosclerosis and hypertension is the underlying cause in the majority of cases.

An early description of medial changes in dissecting aneurysm was given by Babes and Mironescu in 1910,¹³ but received little attention in the literature for several years. In 1928, Gsell¹⁴ described muscular necrosis in spontaneous rupture of the aorta. In 1929 and 1930, Erdheim's papers^{15, 16} appeared, defining idiopathic cystic medial necrosis. His cases were characterized by changes limited to the media, including (1) focal necrosis with dropping out of nuclei, (2) mucoid change in the ground substance and cyst formation, (3) focal destruction of elastic fibers, and (4) repair by fibrosis

without notable vascular proliferation. He emphasized the differences between the changes he observed and those of syphilitic aortitis. Soon a number of cases of dissecting aneurysm were reported with these changes.^{17, 18} Shennan,¹⁹ in 1934, published a monumental review of dissecting aneurysm, analyzing 300 cases, 17 of them his own. Although he was apparently not aware of Erdheim's work, he emphasized the importance of medial changes, and concluded that "A factor common to all cases is degeneration of the elements of the media." The descriptions of the microscopic changes in a number of his cases and several of his photomicrographs strongly suggest cystic medial necrosis. Shennan characterized 79 of his 300 collected cases as being "old" or "healed," but his criteria for this designation are not defined; many of the patients died of progressive dissection, and nearly all of cardiovascular disease. Gore in 1952^{20, 21} published an extensive report of the pathologic findings in 72 cases, all of which showed underlying changes in the media. Gore described 2 forms of medial degeneration: the elastic type, similar to that described by Erdheim, occurring chiefly in younger age groups, and the muscular type, occurring at older ages. He suggested that the primary change in dissecting aneurysm is intramedial dissection of hemorrhage from the vasa vasorum, which only secondarily ruptures through the intima into the lumen.

Later, Gore²² pointed out that 32 of his 72 cases occurred in patients less than 40 years of age, and emphasized the frequency of the condition in youth. A number of cases in children and adolescents have been reported.^{23, 24} Many of them were associated with the skeletal changes of Marfan's syndrome.

In 1896, Marfan²⁵ described a syndrome of musculoskeletal anomalies, including pigeon breast, abnormally long and slender extremities, and changes in the skull and palate. Since the original description a number of other stigmata have been added to the syndrome, including congenital anomalies of the eye and heart, and, more recently, fusiform aneurysm of the aorta²⁶ and dissecting aneurysm.²⁷ Cystic medial necrosis of the elastic type has been associated with Marfan's syn-

drome, and presumably accounts for the aneurysmal changes.^{28, 29} It has even been suggested²⁵ that cystic medial necrosis may be regarded as a "form fruste" of arachnodactyly or Marfan's syndrome. It is conceivable that there is a common underlying metabolic defect, which, in a mild form, is reflected anatomically only in the cardiovascular system, while in its severe form produces widespread changes in many organ systems.

Dissecting aneurysms occasionally communicate by 2 or more rents in the intima with the original lumen of the aorta, forming the so-called "double-barreled aorta."^{2, 19} In these cases the secondary channel sometimes remains patent, and the new channel forms an endothelial lining.^{3, 5} It is from this group that the majority of long survivals have been reported.¹⁻⁷

Although a number of cases have been reported as examples of "healed" dissecting aneurysm, many of these represent only a relatively prolonged survival in the face of a progressive disease process. Only 4 of Gore's 85 cases were healed.²⁰ Most of the reported cases suffered an acute clinical episode of dissection, which was often associated with pain, and then survived for months or years, usually symptomatic, and often incapacitated. A notably frequent sequel to dissecting aneurysm is congestive heart failure, symptoms of which are noted in nearly all patients who survive. Many patients die in intractable failure,⁴ despite the absence at autopsy of obvious cause, such as valvular involvement or myocardial disease. Peery³ suggested that the loss of normal aortic elasticity following dissection results in circulatory failure by impairing the diastolic rebound mechanism, which normally makes an important contribution to circulatory efficiency.

It has been noted²⁰ that although severe pain is a characteristic of dissecting aneurysm, approximately 50 per cent of reported cases are entirely painless throughout their course.

The case described above shows several unusual features and a number that are at variance with the traditional view of dissecting aneurysm as a degenerative disease of old age. The patient's only definite clinical manifesta-

tions of vascular disease were the systolic and diastolic murmurs, the peripheral signs of aortic insufficiency, and the recurrent episodes of atrial fibrillation. The attacks of syncope may have been due either to the aneurysm or to the metastatic melanoma later found in the central nervous system. Excepting possibly the episodes of syncope, the patient never had symptoms of cardiovascular disease; notably, there were no signs or symptoms of congestive heart failure, although he was ambulatory until the preterminal stages of his neoplastic disease.

The clinical findings suggest a degree of aortic insufficiency despite the paucity of anatomic changes in the valve at autopsy. It must have been mild, however, in view of the borderline left ventricular hypertrophy. Several authors have noted and commented on the presence of clinical signs of aortic insufficiency in cases of dissecting aneurysm where autopsy fails to reveal significant anatomic changes.^{1, 4} It might be speculated that much of the elevation in pulse pressure is due to loss of elasticity of the aorta with resultant loss of the diastolic recoil phenomenon.

The patient was relatively young and active until incapacitated by his tumor. He was not hypertensive, and at autopsy showed only minimal evidence of arteriosclerosis. On the other hand, the characteristic changes of idiopathic cystic medial necrosis were conspicuous in all sections taken from the aorta. The medial change was chiefly of the type described by Erdheim, or of the "elastic type" in Gore's classification, although considerable muscular necrosis was also present. The present case supports the increasingly accepted view that essentially all cases of dissecting aneurysm occur in aortas affected by cystic medial necrosis, and that dissection bears no relation to intimal disease and arteriosclerosis.

The dissection in the present case was completely healed, and the false channel was endothelialized. The dissection was associated with a fusiform dilatation of the involved portion of the aorta, a finding that is not uncommon. It is notable that the false channel was dilated, while the original aortic lumen retained its normal dimensions and was about three-fourths surrounded by the false lumen.

SUMMARY

A case of healed dissecting aneurysm of the aorta is reported. The aneurysm produced few clinical manifestations and the patient died of unrelated causes.

The literature on dissecting aneurysm is briefly reviewed. Although the condition has long been recognized, it has only recently been related to the morphologically specific cystic medial necrosis, which is coming to be recognized as the most important underlying cause, rather than arteriosclerosis and hypertension. A number of cases of "healed" dissecting aneurysm have been reported, most of them surviving a limited period of time and succumbing to further dissection and rupture or to congestive heart failure.

Several unusual features of the present case are discussed.

SUMMARIO IN INTERLINGUA

Es reportate un caso de curate aneurysma dissecante del aorta. Le aneurysma produceva pauc manifestationes clinic, e le patiente moriva ab altere causas.

Es presentate un breve revista del litteratura de aneurysma dissecante. Ben que le condition ha ab longo essite recognoscite, il es solo recentemente que illo esseva relationate con le morphologicamente specific necrosis cystic medial, le qual—plus tosto que arteriosclerosis e hypertension—se revela de plus in plus como le major causa primari. Le litteratura cognosce un numero de casos de "curate" aneurysma dissecante. In le majoritate de illos, le patientes superviveva un periodo limitate de tempore e succumbeva a dissection additional con ruptura o a congestive disfallimento cardiac.

Plure aspectos inusual del presente caso es discutate.

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ORGANIZATION IN RESEARCH

"The catchword of our post-war times is organization. The individual freedom is our chief asset, the mainspring of the really new ideas, the guarantee of progress. Physiology does not go forward as an ordered line of battle on a continuous front, but must be carried on, as someone has aptly said, as a guerilla warfare against the unknown, conducted single-handed or by quite small units. There is no need for an extensive organization of research, but there is much need for voluntary cooperation on a limited scale between individuals and laboratories. There are many problems which can only be successfully attacked when experimental physiologists cooperate with histologists, with chemists or physicists or with clinicians, and some problems will require the combined efforts of several of these groups, but the affair is always one of local and voluntary cooperation and does not concern us here.

"While I have no faith in the organization on a large scale of research I think there is a wide and fruitful field for organization of what we might term the services behind the front."—A. KROGH. *The Progress of Physiology*, 1929.

Ventricular Arrhythmias after Intravenous Sodium Lactate in Heart Block

By JOHN F. MURRAY, M.D., AND S. H. BOYER IV, M.D.

Molar sodium lactate has been described as a safe and effective agent in the treatment of bradycardia accompanying complete heart block. However, in 12 patients with heart block, hypertonic lactate infusions produced ventricular tachycardia in 6 and an increased idioventricular rate in only 4. Isopropylnorepinephrine was more effective and without such hazard. The effects of alkalosis from molar lactate, 5 per cent sodium bicarbonate, and hyperventilation are compared. Of these 3, lactate was productive of the greatest ventricular acceleration.

SODIUM lactate has recently been advocated in the treatment of bradycardia and asystole associated with complete heart block. Bellet, Wasserman, and Brody¹⁻⁶ reported that 13 out of 16 such patients responded with an increased ventricular rate following the intravenous administration of .5 or 1.0 M sodium lactate. The coincident appearance of ectopic beats was noted in only 1 patient of this group. These authors concluded that intravenously administered sodium lactate was more effective and less toxic than the more commonly used sympathomimetic and vagolytic drugs in the treatment of atrioventricular block.

This report describes the effects of .5 and of 1.0 M sodium lactate given to 12 patients with heart block. Contrary to previous studies, ectopic beats and ventricular tachycardia were often produced. Only 4 patients exhibited increased ventricular rate. Hypertonic sodium bicarbonate solution was given to 3 patients, and the effect is compared with that obtained with lactate. The effects of isopropylnorepinephrine and lactate are also compared. Other studies performed in an attempt to elucidate the mechanism of increase in the ventricular rate are included.

MATERIALS AND METHODS

Eleven patients with complete atrioventricular dissociation and 1 patient with 2:1 block were given .5 and 1.0 M sodium lactate intravenously on 24 occasions. Age, sex, and presence or absence of syncope at the time of treatment are given in table 1.

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With the exception of patient 9 during his second trial of lactate, none of the patients was in overt heart failure when studied. All but 2 patients (8 and 9) are alive at the time of this report. Every patient except 4, 5, and 10 had experienced Adams-Stokes attacks prior to hospitalization. Slow idioventricular rhythm and asystole were mechanisms of syncope in patients 3, 7-9, 11, and 12. Patient 12 was the only one exhibiting a paroxysm of ventricular tachycardia in the control tracing.

Control electrocardiograms were obtained in all cases before lactate infusion. Nearly continuous recordings were made during and in most cases intermittently for at least half an hour after infusion.

Ten patients (1-3, 5, 7-12) received isopropylnorepinephrine (Isuprel) sublingually. Patients 2, 5, and 7 were given 1 or 2 20 mg. doses of the drug. Patient 9 received 20 mg. every 1 to 2 hours when symptomatic; patient 10, 20 mg. every hour with gradual discontinuance the following week; patients 1, 3, 8, 11, and 12, 20 mg. every 3 hours.

Sodium bicarbonate as a 5 per cent solution was administered intravenously on 4 occasions to 3 patients (7, 8, and 11) who had previously received sodium lactate. The amounts given are shown in table 2.

Patients 9, 10, and 12 required external electric stimulation* of the heart, as described by Zoll and co-workers.⁷

CASE REPORTS

Case 1. A 67-year-old white woman with known heart block of 4 years' duration and repeated Adams-Stokes attacks, treated by ephedrine, experienced 4 attacks on the day of hospital admission.

An electrocardiogram on the day of entry showed complete heart block, idioventricular rhythm, and a

* The pacemaker used for this purpose was Model PM-65 of the Electrodyne Company, Norwood, Mass. This device has a monitor of ventricular rate that may be used automatically to signal an asystole of predetermined length and to start external stimulation.

TABLE 1.—Results with Lactate

Case	Age	Sex	Syncope when treated	Ectopic beats/min. control	Hospital day	Lactate			Comment
						Amt. ml.	Rate ml./min.	Molarity	
1	67	F	No	10	2	160	20	0.5	Paroxysmal ventricular tachycardia
				0-2	2	90	13	0.5	Paroxysmal ventricular tachycardia
				0-4	2	80	11	0.5	Paroxysmal ventricular tachycardia
2	65	F	No	0-1	2	300	30	0.5	Bigeminy; increased frequency ectopic beat
3	63	F	Yes	0	1	250	29	0.5	Multifocal ectopic beats. Paroxysmal ventricular tachycardia
4	63	M	No	0-1	7	140	47	0.5	Many multifocal ectopic beats; chest pain
			No	10	7	80	27	0.5	Slight increase frequency ectopic beats; chest pain
			No	10	11	240	25	0.5	Decreased frequency ectopic beats and decreased ventricular rate; 1 paroxysm ventricular tachycardia; chest pain
5	40	F	No	0	OPD	160	20	1.0	2:1 becomes complete block; slow idioventricular rate followed by paroxysmal ventricular tachycardia
6	80	M	No	0	4	140	22	1.0	No change
7	75	M	No	0	3	100	10	1.0	Decreased rate followed by paroxysmal ventricular tachycardia
8	67	M	No	0	22	200	20	1.0	Increased rate: 38 to 46/min.
			No	1-3	5	325	18	0.5	Increased rate: 38 to 44/min.
			Yes	0	7	120	17	0.5	Increased rate: 15 to 37/min.
9	71	M	No	0	7	200	17	0.5	Increased rate: 32 to 41/min.
			Yes	0	5	130	21	1.0	Increased rate: 27 to 43/min.
			Yes	0	8	200	13	1.0	No change; required electric pacemaker
10	42	M	Yes	0	1	130	14	1.0	Asystole during trial; required electric pacemaker
11	67	M	No	0	4	170	12	1.0	Increased rate: 38 to 44/min.
12	73	F	No	0-10*	1	15	30	1.0	Paroxysmal ventricular tachycardia
			No	0	1	60	10	1.0	Paroxysmal ventricular tachycardia
			No	0-10	1	75	10	1.0	Paroxysmal ventricular tachycardia, abolished by electric pacemaker

* Brief paroxysmal ventricular tachycardia.

TABLE 2.—Results with Five Per Cent Bicarbonate

Case no.	Vent. rate		Bicarbonate	
	Control	Max.	Amt. (ml.)	Rate (ml./min.)
7	38	40	200	15
8	15	42	185	19
8	33	42	250	11
11	36	38	185	9

paroxysm of 5 ectopic beats. The following day about 10 ectopic beats per minute (fig. 1A) were present just before the administration of 160 ml. of .5 M sodium lactate in 8 minutes. Three minutes after beginning this infusion paroxysms of ventricular tachycardia appeared (fig. 1B) that ended about 5 minutes after stopping the infusion (fig. 1D). Thereafter an occasional ectopic beat occurred.

Following a second infusion of 90 ml. of .5 M lactate, given in 7 minutes and begun 14 minutes after the end of the first infusion, ventricular tachycardia promptly developed. The ectopic beats disappeared within 5 minutes of stopping the infusion. With a final infusion of 80 ml. of .5 M lactate, given in 7 minutes and begun 10 minutes after the end of the second infusion, ventricular tachycardia reappeared within 4 minutes and persisted, on 1 occasion, for 30 seconds. At no time, with any of the infusions, was there an increase in basic ventricular rate.

The patient was given 20 mg. of isopropylnor-epinephrine every 3 hours during the remainder of her hospitalization and experienced no further syn- copal attacks.

Case 2. A 65-year-old white woman with a history of bradycardia for 11 years, a myocardial infarction 3 years ago, and syncope attacks for the last 3

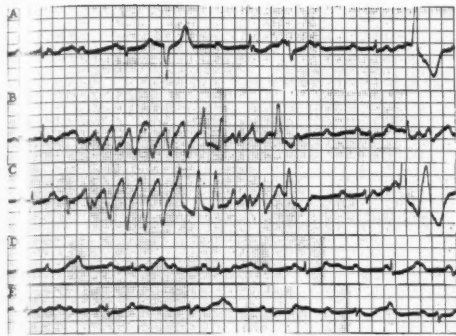


FIG. 1. Case 1, first trial. *A.* Control tracing, showing multifocal ventricular ectopic beats. Ventricular rate (exclusive of ectopic beats) 43 per minute as calculated from R-R interval. *B.* Three minutes after starting 160 ml. of .5-molar sodium lactate at 20 ml. per minute. Note paroxysm of ventricular tachycardia. *C.* Six minutes after starting infusion. Paroxysms of ventricular tachycardia continue. 120 ml. of .5 M lactate given. *D.* Five minutes after stopping infusion. Note ventricular rate unchanged since control. *E.* Thirteen minutes after stopping infusion, ventricular rate unchanged.

years, was admitted to the hospital in a semistuporous condition and with congestive heart failure.

Complete heart block, atrial fibrillation, and an atrioventricular nodal rhythm of about 44 beats per minute were demonstrated by an electrocardiogram.

The patient was treated by phlebotomy, diuretics, and oxygen with moderate improvement. Intravenous atropine, 0.3 mg., produced vomiting and an increase in heart rate from 44 to 56 nodal beats per minute; 20 mg. of isopropyl norepinephrine had little effect.

On the second hospital day repeated electrocardiograms showed a nodal rate of 41 to 43 per minute and very rare ectopic beats. Three hundred milliliters of .5 M sodium lactate were given intravenously in 10 minutes. Although there was no change in nodal rate during or in 40 minutes following administration, ventricular ectopic beats, often bigeminal, appeared in the fourth minute of infusion and persisted for the next 4 minutes.

Two days later signs of a left cerebral vascular accident were noted. After 2 weeks' hospitalization the patient was discharged to her home without specific therapy for heart block.

Case 3. A 63-year-old white woman, known to have a slow pulse rate without syncope for the preceding 2 years, had repeated Adams-Stokes attacks on the day of hospital entry.

An electrocardiogram showed complete heart block without ectopic beats and an idioventricular

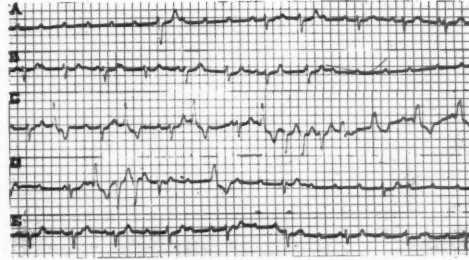


FIG. 2. Case 3. *A.* Control tracing. Patient having seizures during long asystoles. *B.* Two minutes after beginning .5 M lactate at 29 ml. per minute. Note increased ventricular rate followed by asystole lasting 18 seconds. *C.* and *D.* Continuous tracing beginning 7 minutes 33 seconds after starting lactate. Note bigeminy and paroxysms of ventricular tachycardia followed by slow ventricular rate. *E.* Sixteen minutes after completion 250 ml. .5-molar lactate and 5 minutes after 20 mg. isopropyl norepinephrine.

rate of about 24 per minute, frequently interrupted by periods of asystole (fig. 2A) as long as 12 seconds in duration during which she convulsed. She was given 250 ml. of .5 M sodium lactate in 8½ minutes. Periods of asystole (fig. 2B) up to 24 seconds' duration continued to occur until the fifth minute of infusion. Thereafter ventricular ectopic beats appeared and steadily increased in frequency until the majority of beats were extrasystoles, often forming runs of ventricular tachycardia (figs. 2C and D). Sixteen minutes after completion of the lactate infusion and 5 minutes after receiving 20 mg. of isopropyl norepinephrine, the ventricular rate was 44 per minute with a varying R-R interval (fig. 2E).

The patient received 20 mg. of isopropyl norepinephrine every 3 to 4 hours and had no further Adams-Stokes during a 1-month period of observation.

Case 4. A 63-year-old white man, known to have had a myocardial infarction 12 years ago and complete heart block without syncope for 4 years, entered the hospital with congestive heart failure. He became essentially asymptomatic after treatment with digitalis, diuretics, salt restriction, and rest.

On the seventh hospital day an electrocardiogram showed complete heart block, an idioventricular rate of about 44 per minute, 3 different forms of QRS, and at the most 1 ectopic beat per minute. An infusion of 140 ml. of .5 M sodium lactate was given in 3 minutes. Within 2 minutes of beginning the infusion the majority of beats were ectopic and the patient complained of retrosternal pain. Seven minutes after stopping the infusion the number of ectopic beats had decreased to 8 per minute. The idioventricular rate, as calculated from the R-R

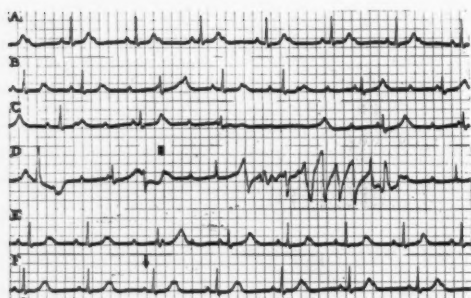


FIG. 3. Case 5. A. Control tracing showing 2:1 atrioventricular block and ventricular rate of 41 per minute. B. Seven minutes and 33 seconds after starting molar lactate at 20 ml. per minute. Note 2:1 block still present in first 2 ventricular complexes (ventricular rate 47 per minute); thereafter atrioventricular block increased and a slow idioventricular rhythm developed (third, sixth, and seventh beats). The fourth and fifth complexes are probably supraventricular in origin. C. and D. Continuous tracing beginning 7 minutes and 53 seconds after starting lactate. Note slowing of ventricular rate, ventricular ectopic beats, and paroxysm of ventricular tachycardia. The bar marks completion of 160 ml. molar lactate, given in 8 minutes. E. Six minutes after stopping lactate. Note reappearance of 2:1 atrioventricular block interrupted briefly by complete block and 2 idioventricular beats (third and fourth complexes). Ventricular rate, at end of strip, 48 per minute. F. One hour after E. Ventricular rate 42 per minute (first 2 complexes). Arrow marks held inspiration. The resultant equal slowing of atria and ventricles indicates 2:1 rather than complete atrioventricular block.

interval, at no time changed more than 2 beats per minute.

Half an hour after stopping the first infusion a second infusion of .5 M lactate was begun. Eighty milliliters were given in 3 minutes with a prompt increase in ectopic beats from about 10 to 15 to 23 per minute and reappearance of chest pain. Frequent ectopic beats persisted for half an hour.

On the eleventh hospital day a control electrocardiogram showed an idioventricular rate of 50 per minute and about 10 ectopic beats per minute. Two hundred and forty milliliters of .5 M lactate were given in 9½ minutes. At the end of this time ectopic beats were 2 per minute and idioventricular rate 43 per minute. Five minutes after stopping the infusion the patient had a brief paroxysm of 5 ectopic beats and complained of retrosternal pain. Thirty minutes after stopping the infusion ventricular rate had gradually increased to 46 per minute and ectopic beats had disappeared.

Throughout hospitalization chest pain was only experienced during lactate infusion. No other cardioacceleratory drugs were given.

Case 5. A 40-year-old white woman was admitted to the hospital complaining of chest pain and mild breathlessness of 5 days' duration. She had received digitalis before admission.

Repeated electrocardiograms showed a ventricular rate of 30 to 50 per minute and varying, but always with second degree heart block. No consistent change in degree of block or ventricular rate was observed after oral potassium chloride, 1.0 mg. of subcutaneous atropine, 25 mg. of oral ephedrine, or 20 mg. of isopropyl norepinephrine. Following 0.5 mg. of intravenous epinephrine atrioventricular block changed from 4:1 to 2:1.

Patient became asymptomatic in the hospital and was discharged to her home. No definite diagnosis of underlying heart disease was made.

Three weeks after discharge she was given 160 ml. of 1.0 M sodium lactate in 8 minutes. A control electrocardiogram showed 2:1 atrioventricular block, with a ventricular rate of 41 per minute and no ectopic beats (fig. 3A). The 2:1 block 7½ minutes after beginning infusion persisted, but ventricular response had increased to 47 per minute. Almost immediately thereafter atrioventricular block became complete and a slow idioventricular rhythm appeared (figs. 3B and C). The lactate was stopped, but within a few seconds a paroxysm of ventricular tachycardia occurred (fig. 3D) and the patient complained of nausea and lightheadedness. The ectopic beats stopped and 2:1 block reappeared about 6 minutes after the end of the lactate (fig. 3E and F).

Case 6. An 80-year-old white man with known complete heart block for several years entered the hospital with mild congestive heart failure. Two episodes of syncope occurred in the preceding 5 years. Congestive failure responded fairly well to diuretics, salt restriction, and rest.

Just before the administration of molar sodium lactate on the fourth hospital day an electrocardiogram showed complete heart block, an idioventricular rate of about 46 per minute, with QRS of 2 different forms, and no ectopic beats. Administration of 140 ml. of molar lactate in 6½ minutes had no effect on the heart rate. No other cardioacceleratory drugs were given.

Case 7. A 75-year-old white man entered the hospital in a semicomatose condition, having had repeated convulsions on the day of entry.

An electrocardiogram showed complete heart block with many ventricular ectopic beats and an idioventricular rate of 36 per minute. Subsequently runs of asystole lasting as long as 1½ minutes appeared. Thereafter a variety of agents, including an unknown amount of molar sodium lactate, procaine amide, isopropyl norepinephrine, and potassium chloride, were given. Sixteen hours after entry the patient was conscious, the heart rate was 50 per minute, and Adams-Stokes attacks had stopped.

At that time all medication was discontinued. A monitor-pacemaker was attached but no electric stimulation was given.

On the third hospital day 100 ml. of molar sodium lactate were given in 10 minutes. A control electrocardiogram showed an idioventricular rate of 39 per minute and no ectopic beats (fig. 4A) during a 4 minute period. Four minutes after starting the infusion the ventricular rate, as calculated from the R-R interval, had slightly decreased (fig. 4B). Lactate was stopped upon the appearance of ventricular tachycardia (fig. 4C). Ectopic beats disappeared about 7 minutes after end of the infusion (fig. 4, D and E). With recovery from ventricular tachycardia the ventricular rate increased to 44 per minute (fig. 4F).

The patient vomited blood on the twelfth hospital day, and a few hours later asystole developed. The heart beat was restored by a slap on the chest. Several blood transfusions were given during the next 24 hours.

On the fourteenth hospital day 200 ml. of 5 per cent sodium bicarbonate were given in 13 minutes (table 2). The ventricular rate increased from 38 to 40 per minute. No ectopic beats appeared.

On the twenty-second hospital day 200 ml. of molar sodium lactate were given in 10 minutes. The heart rate increased from 38 to 46 ventricular beats per minute. Only 2 ectopic beats were observed. Serial electrolyte and pH determinations were made (table 3).

When last seen on the thirtieth hospital day the patient had been transferred to the surgical service with a partial large bowel obstruction of unknown etiology. He remained free of syncopal attacks.

Case 8. A 67-year-old white man, known to have complete heart block for 3½ years and Adams-Stokes attacks for 6 months, entered the hospital because of increased frequency of syncopal attacks.

Isopropyl norepinephrine, 20 mg. every 3 hours during waking hours, markedly diminished the frequency and severity of attacks.

On the fifth hospital day an electrocardiogram showed complete heart block, an idioventricular rate of 38 to 40 per minute, and 1 to 3 ectopic beats per minute. Half-molar sodium lactate, 325 ml., was given in 18 minutes. A maximum ventricular rate of 43 to 44 per minute appeared 5 minutes after the end of infusion and 1 ectopic beat per minute was present. Twenty-three minutes after completion of the infusion the rate had returned to 38 to 39 per minute.

On the seventh hospital day isopropyl norepinephrine was withheld for 4 hours. The ventricular rate was 15 to 17 per minute with periods of asystole up to 6 seconds in duration. No ectopic beats were present. The patient was conscious but very weak and faint. Then 120 ml. of .5 M sodium lactate were given in 7 minutes. Within 3 minutes the ven-

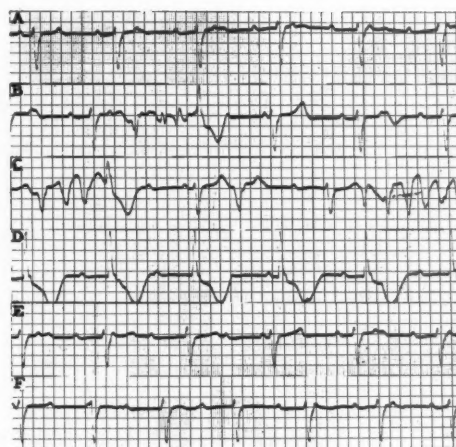


FIG. 4. Case 7. A. Control tracing. Ventricular rate 39 per minute. B. After nearly 50 ml. molar sodium lactate in 4 minutes 45 seconds. Note ventricular rate, exclusive of ectopic beats, is slower than in control. C. Thirty seconds after completion of 100 ml. molar sodium lactate in 10 minutes. Note paroxysms of ventricular tachycardia. D. Three minutes after completing infusion. New ventricular pacemaker 37 per minute. E. Eleven minutes after completing infusion. Note original pacemaker has returned at 38 per minute. F. Sixteen minutes after infusion. Ventricular rate 44 per minute.

TABLE 3.—Electrolyte Studies in Case 7

Time min.	pH	CO ₂ mEq./L.	Na mEq./L.	K mEq./L.	Cl mEq./L.	Vent. rate per min.
↑ 0	7.40	21.56	133	4.60	109	38
200 ml. M Lactate						
↓ 10	7.44	22.45	152	3.88	106	36
20	7.45	24.24	144	4.10	106	43
30						46
35	7.49	24.64	143	4.55	106	45
80						43

tricular rate was 29 per minute and the patient felt stronger. A maximum rate of 37 per minute appeared 3 minutes after stopping the infusion. Ten minutes later the rate had fallen to 32 to 33 per minute, at which time an additional 200 ml. of .5 M sodium lactate were given in 12 minutes. A maximum rate of 41 per minute was attained 6 minutes after starting the infusion.

On several occasions administration of 20 mg. of isopropyl norepinephrine increased ventricular rate by amounts varying from about 18 per minute to 30 per minute, within 3 to 4 minutes.

The patient was discharged from the hospital and was essentially asymptomatic while taking 20 mg. isopropylnorepinephrine every 3 hours.

He returned to the hospital for further study. Hyperventilation at 12 respirations per minute was performed for 3 minutes. Within a minute of starting this maneuver the ventricular rate increased from about 29 per minute to 37 per minute. Upon discontinuing hyperventilation the increased rate persisted for 9 seconds then was followed by a marked slowing of ventricular rate to 4 beats, with a new QRS form in the next 21 seconds, during which he had an Adams-Stokes attack. During this attack, at a time when ventricular rate was 15 per minute, an infusion of 185 ml. of 5 per cent sodium bicarbonate solution was begun that required 10 minutes for completion (table 2). Within 1½ minutes after beginning the infusion the original QRS form returned at 29 beats per minute. A maximum rate of 42 per minute appeared 3 minutes after completing the infusion and persisted for at least half an hour.

On another occasion intravenous administration of 250 ml. of 5 per cent sodium bicarbonate solution in 23 minutes caused the ventricular rate to increase from a control rate of 33 per minute to 42 per minute 18 minutes after starting the infusion.

Subsequently, on the same day 2 trials of hyperventilation at 12 respirations per minute caused prompt increase in ventricular rate from 31 to 36 and from 32 to 37 per minute. These effects disappeared within 2 to 5 minutes after stopping overbreathing and the rate returned to about 32 per minute.

Several months after these studies the patient died under circumstances unknown to us. At autopsy, coronary vessels were reported to be nearly normal.

Case 9. A 71-year-old white man first developed complete heart block and Adams-Stokes attacks 1 year before the present entry. Following treatment with ephedrine and isopropylnorepinephrine his rhythm reverted to a sinoatrial pacemaker. He remained well until the day of his last entry, when he again had a syncopal attack and was found to have complete heart block. He was treated with 10 to 20 mg. of isopropylnorepinephrine every 1 to 2 hours and 0.3 mg. of atropine subcutaneously every 4 hours.

The rhythm included a period of complete heart block with a ventricular rate of 40 per minute, 2:1 block, and sinus rhythm. No ectopic beats were observed.

On the fifth hospital day isopropylnorepinephrine was omitted and 2½ hours later, during a syncopal episode, he was given 130 ml. of molar lactate, with an increase in ventricular rate from 27 to 43 per minute and an accompanying disappearance of symptoms. No ectopic beats were present. Twenty-

nine minutes after the end of infusion the ventricular rate had decreased to 35 per minute. On the seventh hospital day acute pulmonary edema developed and was successfully treated by morphine, oxygen, and phlebotomy. On the eighth hospital day a long period of cardiac arrest appeared, and 200 ml. of molar sodium lactate, begun at once, was given intravenously in a 15-minute period. The external electric pacemaker was used at the same time as the lactate in order to facilitate circulation of the infused material. In spite of the infusion, discontinuance of the electric pacemaker resulted in a systole; pulmonary congestion that was present before the infusion increased.

The external pacemaker was employed almost continuously for the next 24 hours. Intravenous epinephrine was administered and 2:1 heart block reappeared. On the ninth hospital day asystole again appeared that was unresponsive to external stimulation and epinephrine. Permission for autopsy was refused.

Case 10. A 42-year-old Negro with a history of paroxysmal tachycardia for 5 years entered the hospital with persistent tachycardia of several days' duration. More than 2.0 Gm. of digitalis leaf had been given in the 3 days before admission and 0.2 mg. of lanatoside C (Cedilanid) was given in the emergency room.

Electrocardiograms showed ventricular tachycardia of about 220 beats per minute. With the administration of a total of 1.0 Gm. of procaine amide intravenously the heart rate gradually slowed to 150 per minute. One hour later the patient suddenly convulsed and the electrocardiogram showed ventricular asystole. Repeated blows to the chest restored the heart beat momentarily. When this became ineffective direct stimulation of the myocardium with a needle with and without epinephrine produced ventricular contractions. A ventricular rate of 30 to 60 per minute was maintained by an infusion of about 2 to 4 µg. of epinephrine per minute. Complete heart block alternating with varying second degree block was present. The patient was conscious and comfortable. A pacemaker-monitor was attached.

Three hours after the development of asystole epinephrine was slowly discontinued and complete heart block became constant. Atropine, 1 mg. intravenously, had no effect. In the next 45 minutes the ventricular rate gradually decreased; when it was 19 per minute with the patient semiconscious, 130 ml. of molar sodium lactate were given in 9 minutes. During the infusion the ventricular rate continued to slow, and long asystoles, together with convulsions, developed. The external electric cardiac pacemaker was employed almost continuously for the next 15 minutes. Twenty milligrams of isopropylnorepinephrine were given; within 7 minutes the ventricular rate was 50 per minute.

TABLE 4.—Electrolyte Studies in Case 11

Time min.	pH	CO ₂ mEq./L.	Na mEq./L.	K mEq./L.	Cl mEq./L.	Vent. Rate per min.
0	7.40	22.16	134	4.30	107	38
5	7.42	24.51	143	3.85	101	38
170 ml. M Lactate.						
10	7.45	25.43	147	3.58	107	37
14	7.44	24.43	148	3.63	103	38
24	7.45	27.49	142	3.85	105	43
27						44
54						41
84	7.45	27.92	139	3.70	109	38

Complete heart block, second degree block, and normal sinus rhythm were variously present for the next 4 days. Several episodes of asystole occurred during this time. Twenty milligrams of isopropyl-norepinephrine every hour were necessary for the first few days in order to prevent periods of asystole. The drug was gradually discontinued when normal sinus rhythm was persistent.

The patient was discharged after 3 weeks' hospitalization, asymptomatic and without medication.

Case 11. A 67-year-old man with known heart block and Adams-Stokes attacks for at least 3 years entered the hospital because of increasing frequency of syncope. Shortly after entry isopropyl-norepinephrine, 20 mg. every 3 hours, was begun; the ventricular rate increased from 36 to 40 per minute to 44 to 48 per minute and no further attacks appeared.

On the fourth hospital day 170 ml. of molar sodium lactate were given in 14 minutes. No other medication had been given in the preceding 3 hours. A control electrocardiogram showed complete heart block with an idioventricular rate of about 38 per minute and no ectopic beats. Ten minutes after stopping the infusion the ventricular rate had reached a maximum of 44 per minute. No ectopic beats appeared. Eighty-four minutes after beginning the infusion, heart rate had returned to control levels. Serial electrolyte and pH determinations were obtained (table 4).

The following day 185 ml. of 5 per cent sodium bicarbonate were given in 20 minutes (table 2). No other medication had been given in the preceding 6 hours. A control electrocardiogram showed an idioventricular rate of 36 per minute. The rate increased to 38 per minute 2 minutes after stopping the infusion.

Case 12*. A 73-year-old white woman with known complete heart block and repeated Adams-Stokes

* We wish to thank Dr. George Schwartz, Brooklyn, N. Y., for allowing us to study this patient.

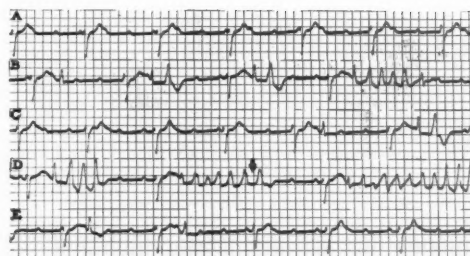


FIG. 5. Case 12, first trial. A. Control tracing. Ventricular rate 35 per minute. B. Control showing ectopic beats and the only paroxysm of ventricular tachycardia in a 4-minute tracing. C, D, and E. Nearly continuous tracing beginning 14 seconds after starting molar sodium lactate. The arrow marks the completion of 15 ml. lactate in 30 seconds. Note paroxysms of ventricular tachycardia in D. Ventricular rate at end of E unchanged since control.

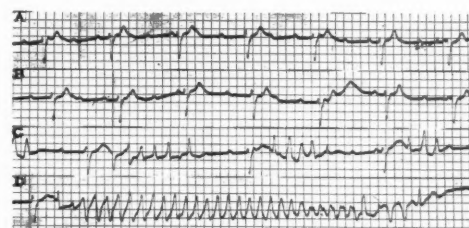


FIG. 6. Case 12, second trial. Same patient as in figure 2. A and B. Continuous control tracing in minute prior to starting lactate. Note absence of ventricular ectopic beats. Ventricular rate 36 per minute. C and D. Continuous tracing 2 minutes after starting molar lactate at 10 ml. per minute. Note paroxysms of ventricular tachycardia.

attacks for 3 years experienced 3 such attacks on the day of hospital entry. During many such episodes her private physician had found no pulse or heart sounds. Frequent electrocardiograms in the past 3 years showed isolated ventricular ectopic beats but never ventricular tachycardia.

An electrocardiogram on admission demonstrated 21 ectopic beats in 4 minutes including 1 paroxysm of 6 such beats (figs. 5A and B). Fifteen milliliters of molar sodium lactate were given in a 30-second period and a number of paroxysms of ventricular tachycardia appeared (figs. 5C, D, and E). There was no change in basic ventricular rate. The patient denied previous such palpitations. The heart sounds were audible by auscultation during the paroxysms.

A second infusion of 60 ml. of molar lactate was then administered in 6 minutes. The number of ectopic beats promptly increased from 0 to 16 to 42 per minute, usually appearing in paroxysms of ventricular tachycardia (fig. 6). The runs of tachy-

cardia persisted but gradually decreased in frequency during the following 28 minutes. Suddenly the frequency and duration of the paroxysms increased and for the first time were associated with convulsions. It was then noted that the infusion was again flowing and that 75 ml. of molar lactate had inadvertently been administered to the patient in the preceding 7 to 10 minutes. For 20 minutes there were continued paroxysms of ventricular tachycardia and numerous accompanying convulsions. External cardiac stimulation with the electric pacemaker was applied during a brief period when idioventricular rate was about 48 per minute. Stimulation was continued for 2½ minutes at 60 beats per minute following which there were no further paroxysms for the next half hour. Several paroxysms without convulsions were noted over the next 13 hours but external stimulation was not required.

During the remainder of her hospitalization the patient received 20 mg. of isopropyl norepinephrine every 3 hours. The ventricular rate remained between 33 and 50 per minute with only occasional ectopic beats and no further Adams-Stokes attacks.

RESULTS

Lactate

The results together with the amount and rate of lactate administration are listed in table 1. The responses may be conveniently divided into 4 categories, as listed below. Three patients (4, 7, and 9) exhibited a different response on successive occasions and therefore appear in 2 categories.

Increased Ventricular Rate without Ectopic Beats. Four patients are included in this group (8, all trials; 9, first trial; 7, second trial; and 11). Patients 8 and 9 were treated during syncopal episodes and responded with increased ventricular rates and cessation of symptoms; both had made equally prompt and satisfactory recoveries with isopropyl norepinephrine on previous occasions. Patient 9 was subsequently treated with 200 ml. of molar sodium lactate during bouts of prolonged asystole and failed to respond until stimulated with an external electric cardiac pacemaker. He is therefore also included in the last group.

Increased Frequency of Ectopic Beats. Two patients, 2 and 4 (first and second trials), had ventricular ectopic beats in the control electrocardiograms that increased in frequency and became multifocal. Ventricular tachycardia did not appear.

Paroxysmal Ventricular Tachycardia. The

most striking effect was the production of frequent paroxysms of ventricular tachycardia in 5 patients (1, 3, 5, 7, and 12) on 9 occasions. Patient 4, who had previously manifested an increased frequency of ectopic beats (on 2 occasions) following lactate infusion, on the third trial had an initial decrease in ectopic activity and in the idioventricular rate followed by a single paroxysm of ventricular tachycardia 5 minutes after the completion of the infusion.

Patients 1 (fig. 1) and 12 (figs. 5 and 6) had ventricular ectopic beats in control tracings that increased in frequency during the infusion and were followed by ventricular tachycardia on 3 trials in both patients. Patients 5 (fig. 3) and 7 (fig. 4) showed no ventricular ectopic beats in control electrocardiograms taken for at least 4 minutes. Patient 3 (fig. 2) was having syncopal attacks and the control tracing was limited to 1½ minutes during which no ectopic beats were observed.

In 2 patients (1 and 12) there was no change in the ventricular rate, as calculated from the R-R interval and exclusive of ectopic beats, prior to the onset of ventricular tachycardia. In 3 patients (4, 5, and 7) there was a slowing in the idioventricular rate before the appearance of ventricular tachycardia. Patient 4 had a decrease from 50 to 42 beats per minute. Patient 5 (fig. 3) had an initial increase in the sinoatrial rate with a resultant change from 41 to 47 ventricular responses per minute; at the end of the infusion the existing 2:1 block suddenly became complete and a slow idioventricular rate developed that was rapidly followed by multifocal ectopic beats and short paroxysms of ventricular tachycardia.

Patient 7 (fig. 4) was given lactate on the third hospital day and responded initially with a decreased idioventricular rate followed by multifocal ectopic beats and ventricular tachycardia. Nineteen days later he was given twice as much lactate at twice the rate and responded with an increase in ventricular rate from 38 to 46 contractions per minute without the appearance of ectopic beats.

Only 1 (patient 3) of this group had an increase in idioventricular rate before developing ventricular tachycardia; however,

long asystoles continued to occur in this patient (figs. 2B and D).

In every patient except 12 (figs. 5 and 6) ventricular tachycardia disappeared within a few minutes of stopping the infusion. Patient 12 continued to have paroxysms of ventricular tachycardia and syncope for at least 13 hours after discontinuing the lactate therapy. Prior to this hospitalization, the mechanism of the Adams-Stokes attacks was thought to be asystole.

No Change or Slowing. Patient 6 showed no increase in the rate of ventricular contractions originating in 2 foci of nearly similar rate and seen in the control records. Patient 9 failed to respond on his second trial during bouts of asystole until external stimulation was applied as already described. Pulmonary congestion was present in this case and became worse following 200 ml. of molar sodium lactate. Patient 10 had a gradual fall in ventricular rate from 24 to 19 per minute during a 45 minute control period. Then 130 ml. of molar sodium lactate were given in 9 minutes to this patient. While the infusion was running, he had a prolonged period of asystole and a convulsion that lasted until external cardiac stimulation was applied.

Isopropylnorepinephrine

Isopropylnorepinephrine was without effect on the ventricular rate in patients 2 and 5. The drug was given in combination with too many other agents in patient 7 to be properly evaluated. Patient 9 had decreased frequency of Adams-Stokes attacks while receiving this drug. Patients 1, 3, 8, and 10-12 were completely free of syncopal episodes while receiving isopropylnorepinephrine in effective dosage.

In most cases where the drug was effective, 20 mg. every 3 hours by day was sufficient. In patient 8 administration before arising for nocturnal urination was necessary to prevent a syncopal attack that frequently occurred at that time.

In no case was an increased frequency of ectopic beats observed after the administration of isopropylnorepinephrine.

When compared with intravenous lactate, sublingual isopropylnorepinephrine was found

equally effective in increasing ventricular rate in patients 8 and 11. In 4 patients (1, 3, 10, and 12) having no response or increased ectopic activity after lactate, isopropylnorepinephrine abolished Adams-Stokes attacks. In 2 patients (2 and 5) both drugs were ineffective. In no case where the 2 drugs could be compared was lactate effective and isopropylnorepinephrine ineffective.

Bicarbonate

Three patients (7, 8, and 11) received hypertonic sodium bicarbonate. The results are shown in table 2. Only in patient 8 was the increase in ventricular rate comparable to the change after hypertonic lactate. No ectopic beats were noted in any of the trials with bicarbonate.

Other Studies

Hyperventilation. A single patient (8) hyperventilated by increasing the depth of respiration, not the rate, for 3-minute periods. On 3 occasions, there was an increase in ventricular rate from 29 to 37, 31 to 36, and 32 to 37 per minute. However, 9 seconds after completion of the first hyperventilation period there was an abrupt slowing of ventricular rate to about 15 contractions per minute and syncope occurred. This phenomenon was not seen on the 2 subsequent trials following which the increased ventricular rate gradually returned to control levels in 2 to 5 minutes.

Electrolyte and pH Determinations. Arterial blood samples were obtained in cases 7 and 11 for determination of serial changes in carbon dioxide, sodium, potassium, chloride, and pH.* The results together with ventricular rates at appropriate intervals are presented in tables 3 and 4.

DISCUSSION

The data presented show clearly that sodium lactate may cause undesirable ventricular

* Carbon dioxide was determined by the manometric method of Van Slyke and Neill; sodium and potassium were measured by flame photometry with an internal lithium standard; chloride was measured by the method of Schales and Schales⁸; pH was obtained by Beckman glass electrode pH meter, model H-2.

ectopic activity ranging from increased frequency of ectopic beats to paroxysms of ventricular tachycardia. These deleterious effects were found on 13 occasions in 7 patients, and could not be uniformly related to the presence or absence of ectopic activity seen in records obtained prior to the administration of sodium lactate. Four of the 5 patients with ventricular premature contractions in control electrocardiograms exhibited an increase in ectopic beats. However, of the 7 patients without ventricular premature contractions before treatment, 3 showed the prompt appearance of multifocal ectopic beats and paroxysms of ventricular tachycardia.

In some instances, there was a relationship between the amount of sodium lactate given and the rate of infusion to the development of ventricular arrhythmias. Bellet, Wasserman, and Brody⁶ recommended that 20 to 80 ml. of molar sodium lactate be given in $\frac{1}{2}$ to 2 minutes to patients having Adams-Stokes attacks; to asymptomatic patients, doses of 100 to 160 ml. of sodium lactate were to be given in 10 to 15 minutes. The reasons for a maximal rate of infusion were not discussed. Five of our patients (4, first trial; 5-7, second trial; and 12, first trial) were given lactate in excess of these recommendations. Three of the 5 persons exhibited transient increases in ectopic activity. Patient 12, however, revealed an equal tendency to develop ventricular tachycardia on 2 subsequent trials despite a decrease in the rate of infusion (figs. 5 and 6). In patient 4, decreasing the rate of infusion decreased the frequency of ectopic activity. In patient 6, no change from control electrocardiograms was noted in spite of infusing molar sodium lactate at 22 ml. per minute.

Patient 7 clearly demonstrates that the rate and amount of molar lactate administered are not the sole factors responsible for the production of ectopic ventricular rhythms. Shortly before the time of initial study, intermittent syncopal attacks occurred. He responded to the administration of 100 ml. of molar sodium lactate with multifocal ventricular ectopic beats and paroxysms of ventricular tachycardia (fig. 4). The patient became asymptomatic after treatment with salt restriction and

bed rest and was restudied after 19 days of this therapy. He was given twice as much molar sodium lactate (200 ml.) at twice the infusion rate as in the initial test, distinctly in excess of recommended dosage, and his heart rate increased from 38 to 46 beats per minute with only 2 ectopic beats noted early in the trial. It is obvious that reversible factors, probably originating within the myocardium, may profoundly alter the response to the lactate ion. It is not known what these factors are.

Four patients (3, and 8-10) were treated on 5 occasions during syncopal episodes associated with prolonged asystole or very slow idioventricular rates. In patient 3, ectopic beats appeared 5 minutes after beginning an infusion of .5 M lactate at nearly 30 ml. per minute; she was still symptomatic at that point, having had a 24-second period of asystole in the minute preceding the ectopic beats. When given molar lactate at rates of flow and dosage greater than in patient 3, patient 9, in his first trial, had a prompt increase in rate of contractions without ectopic activity. Patient 9 on another occasion and patient 10 when initially treated failed to respond to the equivalent amounts and rates of infusion that produced ventricular tachycardia in patient 4. Patients 9 and 10 required external cardiac stimulation to maintain circulation. Perhaps the rates of infusion were inadequate in the latter cases to produce the desired effect; but it can be seen that equal amounts and rates of administration produce inconstant and possibly hazardous effects in different patients.

We have no explanation for the marked contrast between our results and those reported by Bellet, Wasserman, and Brody. Of their 16 patients with complete heart block, 13 had an increase in ventricular rate following lactate infusion and only 1 developed ventricular extrasystoles.¹⁻⁶ No instances of paroxysmal tachycardia were noted in 30 additional patients with a variety of other types of cardiac rhythm.⁷ Ventricular ectopic beats appeared only 6 times in the total of more than 46 patients tested.^{5, 6}

These authors contrasted the relative safety and efficacy of molar lactate with the dangerous effects produced by sympathomimetic agents,

particularly epinephrine. Ten of our patients received isopropylnorepinephrine, often in large doses; 7 of these responded with increased ventricular rate and without the development of ventricular arrhythmias.

Arterial blood samples obtained before, during, and after administration of molar sodium lactate demonstrated alkalosis and electrolyte shifts that are in no way different from those reported by Singer⁹ using hypertonic sodium bicarbonate and are in accord with the reports of others⁴ using molar sodium lactate. These results establish that there is nothing unique in the over-all effects of sodium lactate. An increase in heart rate was found on several occasions after hyperventilation in 1 patient and in 2 instances in the same patient following the administration of 5 per cent sodium bicarbonate. These limited observations suggest that alkalosis is the determining factor in producing the cardiac effects. However, mole for mole, bicarbonate does not affect the heart as strikingly as lactate. The latter is no better buffer or alkalinizing agent than sodium bicarbonate until metabolized to provide base and raise the pH. Since the myocardium has a very high capacity to utilize lactate,¹⁰ sodium lactate must alter its pH far more than equimolar doses of sodium bicarbonate, with a correspondingly greater change in cardiac irritability and rhythmicity.

SUMMARY

Twelve patients with heart block and bradycardia or asystole were given .5 or 1.0 M sodium lactate on 22 occasions. Contrary to previous reports, molar sodium lactate was found to be much less efficacious and far more hazardous than isopropylnorepinephrine. Increased frequency of ectopic beats developed in 7 patients, of whom 6 developed ventricular tachycardia on 10 occasions. Many of these patients had idioventricular slowing before the appearance of tachycardia. Only 4 patients on 6 occasions had an increase in ventricular rate without developing ectopic beats.

The effects of hypertonic bicarbonate and hyperventilation were compared with the results of lactate infusion in a few patients. The greater magnitude of ventricular rate increase

after lactate suggests that its rapid uptake and utilization by the myocardium promotes greater myocardial alkalosis and altered irritability.

SUMMARY IN INTERLINGUA

Decem-duo patientes con bloco cardiac e bradycardia o asystole recipeva a 22 occasiones administrationes intravenose de lactato de natrium de 0,5 o 1,0 M. In contrasto con previe reportos, lactato de natrium in solution molar se monstrava multo minus efficace e multo plus risce que isopropylnorepinephrina. Augmentate frequentias de pulsos ectopic se disveloppava in 7 patientes. Sex de istes disveloppava tachycardia ventricular a 10 occasiones. Multes de iste patientes habeva retardation idioventricular ante le apparition del tachycardia. Solmente 4 patientes monstrava a 6 occasiones un acceleration ventricular sin le disveloppamento de pulsos ectopic.

Le effectos de bicarbonato hypertonic e de hyperventilation esseva comparate in un certe numero de patientes con le resultados del infusion de lactato. Le plus grande acceleration ventricular post lactato pare reflecter que su rapide acception e utilisation per le myocardio produce plus alte grados de alcalose myocardial e un alterate irritabilitate.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Duroziez' Sign. Paul Louis Duroziez (1826-1897) of Paris wrote of "The Intermittent Crural Double Murmur as a Sign of Aortic Insufficiency" (*Du double souffle intermittent crural, comme signe de l'insuffisance aortique*) in the *Archives générales de Médecine*, 5th series, 17: 417-443 (April), and 588-605 (May), 1861.

"The intermittent crural murmur always accompanies aortic insufficiency, and betrays it in difficult and complicated cases. It is the pathognomonic sign of this condition. Since this has never been said before by any author, I shall proceed to demonstrate the fact. . . . When the crural artery is compressed, the hand perceives a shock, or trembling; with the ear may be heard a bruit which may be represented by the sound *toc* or a peculiar murmur, the intermittent simple murmur. . . . If, after having compressed the artery for some little time, one slowly lessens the amount of compression, a splendid murmur will appear, especially in chlorotic subjects. . . . This is the continuous double murmur.

"But there is another murmur called the intermittent double murmur which is met in certain cases, to which we shall now give special study. . . . There are two methods of producing this double murmur, that is, with the stethoscope or with the hand. One presses gradually with the instrument until the artery is obliterated, and with a certain degree of pressure the double murmur appears . . . or one may apply pressure with the hand alternately both proximal and distal to the instrument with which no pressure is exerted. The proximal pressure produces the first murmur, and distal pressure produces the second murmur. This, however, can only be done when the second murmur is produced with unusual ease."

Electrocardiographic and Plasma Potassium Responses Elicited on Cooling the Chest Wall of Man

By BENJAMIN KAMINER, M.B. AND RALPH E. BERNSTEIN, M.Sc., M.B.

The application of ice to the anterior chest wall in human subjects resulted in retardation of repolarization of the anterior myocardium and was accompanied by a decrease in the plasma potassium. These phenomena were tentatively related to the effects of local cooling of the myocardium.

IT HAS been demonstrated¹⁻⁶ that indirect local cooling of the heart in man produces characteristic electrocardiographic changes analogous to those obtained by direct cooling of the myocardium in experimental animals.⁷⁻¹⁰ In particular, precordial cooling in man causes depression and inversion of the T wave over the site of the cooled myocardium.

In this study the precordium was cooled in 2 ethnic groups, African (Bantu) and European (white South African), in order to gain further information on the factors involved in the production of the altered pattern in the electrocardiogram. An attempt was made to correlate the T-wave changes with the decrease in the serum potassium levels that resulted from precordial cooling. In addition, further observations are presented on the different electrocardiographic response in the African as compared with the European.⁵

METHODS

Ten African and 10 European healthy male students presented themselves for investigation either in the afternoon or morning after 6 to 12 hours of food deprivation; water was permitted ad lib. The subject rested in the reclining position for an initial period of 30 to 60 minutes (basal period). An icebag 10½ inches in diameter was then placed on the anterior chest wall for 1 hour (experimental period). After removal of the icebag the subject remained in the same position for a further 60 minutes (recovery period).

During the basal period, recordings were taken of the arterial blood pressure and skin temperatures over the precordium and ankle, and venous blood was drawn for the chemical and other analyses listed below. At the end of the basal period these procedures were repeated and in addition an electrocardiogram was recorded immediately after the

drawing of the second sample of blood. A baseline having thus been established, the icebag was applied and during the subsequent experimental period all the above procedures were repeated at 15-minute intervals. A final series of observations was made at the end of the recovery period.

The conventional 12-lead electrocardiogram was recorded for 2 respiratory cycles. During the experimental period at the 15-, 30-, and 45-minute intervals, lead V₂ only was used, the electrode being placed under the icebag.

The blood samples drawn at all the intervals mentioned were analyzed for sodium and potassium¹¹ in all the subjects, calcium¹² in 9 subjects, hemoglobin and hematocrit values (the tubes were spun at 3,500 r.p.m., 2,050 G for 45 minutes) in 9 subjects, and glucose according to the Somogyi method in 6 subjects. In 10 subjects the number of eosinophils was determined¹³ in the blood sample drawn after cooling for 60 minutes and was compared with the number in the basal and recovery samples.

Sodium and potassium were also estimated in the urine¹⁴ in 5 subjects during the basal, experimental, and recovery periods. Six subjects either could not void urine or the volumes were insufficient to draw reliable conclusions.

To assess whether the local cooling of the precordium was responsible for the findings to be presented, each student was reinvestigated on a subsequent occasion. Identical procedures were followed in each instance, except that the icebag was placed either on the abdomen or on the lateral aspect of the thigh. This experiment will be referred to as the control. In this control series the temperature readings of the cooled area of skin showed a decrease similar to that obtained over the precordium. The areas of skin cooled were similar in the case of the chest and abdomen, and somewhat less in the case of the thigh.

RESULTS

T Waves

Chest Leads. Depression or inversion of the T wave in lead V₂ was observed 15 minutes after placing the icebag on the chest. The voltage decreased progressively and at the end of the experimental period depression or inversion

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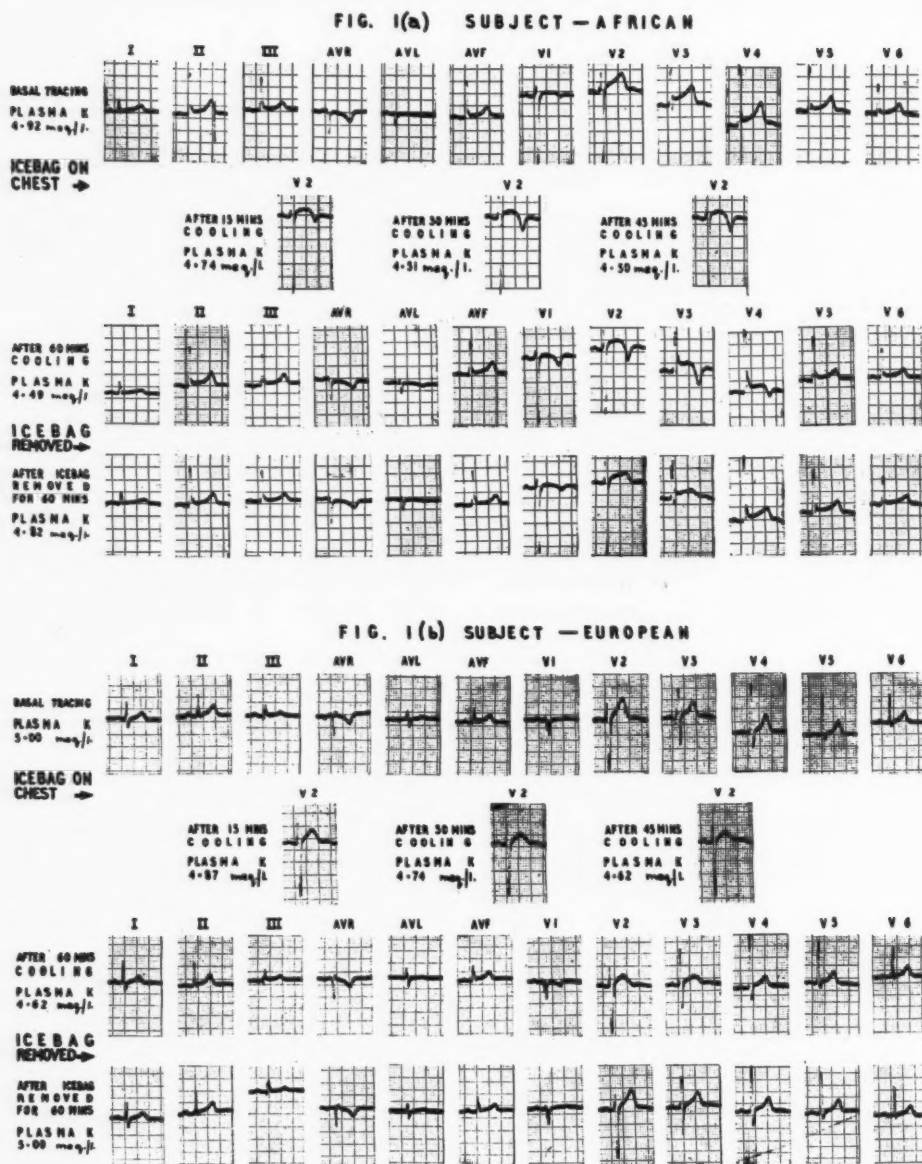


FIG. 1. Serial electrocardiogram tracings and plasma potassium concentrations in an African subject (a) and European subject (b).

of the T wave was found in leads V_1 to V_4 , while leads V_5 and V_6 showed minor or no change. At the end of the recovery period, the average amplitude of the affected T waves returned to a level only slightly below that of the basal height. These serial responses (figs.

1 and 2) were observed in all cases except 1 African. T-wave inversion occurred in leads V_1 , V_2 , and V_3 in 3 Africans (fig. 1a) and in V_1 or V_3 in 2 more Africans. On the other hand, in 5 Europeans the T wave became inverted only in lead V_1 (fig. 1b). In addition, the per-

FIG. 2(a)

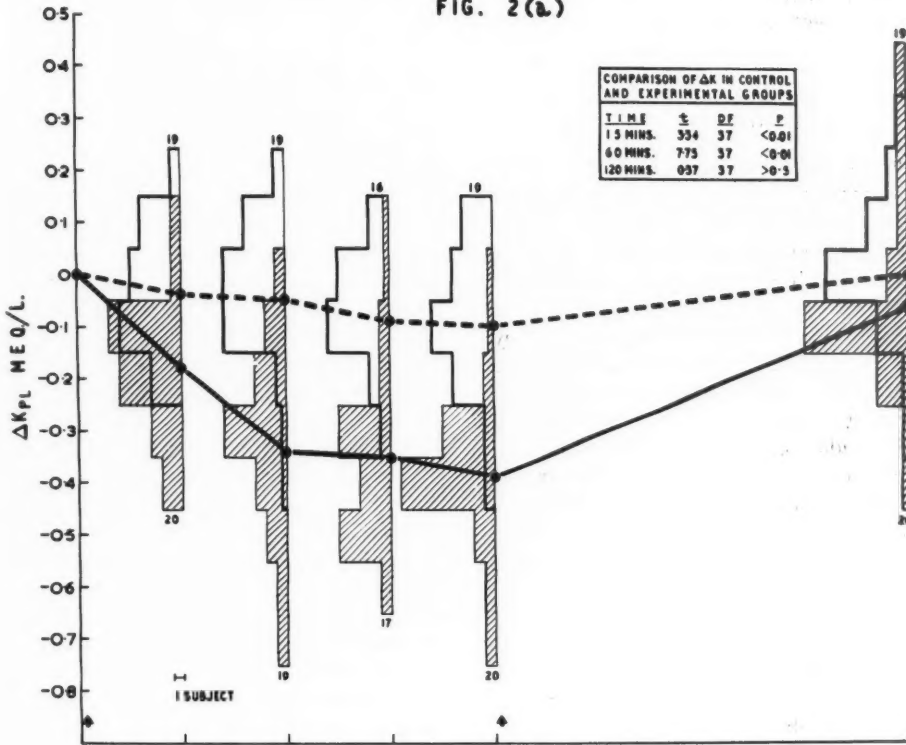


FIG. 2(b)

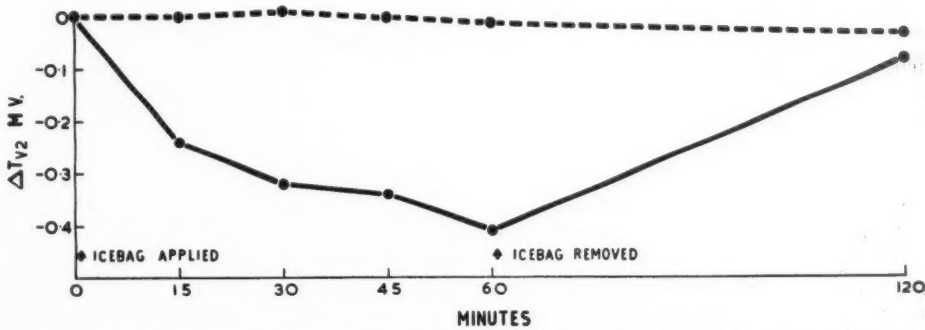


FIG. 2. *a.* Mean decrements of plasma potassium (ΔK_p) in both the control and experimental groups. Crosshatched blocks, experimental; clear blocks, control; continuous line, experimental mean values; broken line, control mean values. Number above the histogram represents number of control observations. Number below represents number of experimental observations. Inset: *t* test. *b.* Mean decrements in T wave in lead V_2 (ΔTV_2) in millivolts (MV) for both control (broken line) and experimental subjects (continuous line).

TABLE 1.—Average Percentage Reductions in Amplitude of T Waves after Sixty Minutes of Precordial Cooling

	Precordial leads			
	V ₁	V ₂	V ₃	V ₄
African.....	68	72	65	57
European.....	99	59	38	31

centage reduction in the amplitude of the T waves (leads V₁ to V₄) in the African and European students (table 1), also illustrates that the area of the myocardium subtended by the electrodes V₂, V₃, and V₄ was affected more in the African than in the European group.

Notching of the descending limb of the T wave in leads V₂, V₃, and V₄ was a striking feature in 5 Africans and 5 Europeans (fig. 1). In one of these subjects the notching preceded inversion of the T wave and in another notching was detected only at the end of the recovery period, having been preceded by inversion of the T wave during cooling. In these 2 subjects the notch and nadir of the inverted T wave were equidistant from the Q wave (fig. 1a; lead V₃, 60-minute cooling and recovery tracings). This observation suggested that the notch is an early stage in the genesis of the inversion.

Limb Leads. Slight depression of the T wave was observed in lead I (7 subjects), lead II (2 subjects), and lead aV_L (10 subjects), with a small increase in positivity in leads III (12 subjects), aV_F (16 subjects), or decrease in negativity in lead aV_R (4 subjects).

Other Modifications in the Electrocardiogram

The P wave became flattened in V₂ in one subject and in leads V₁ and V₂ in another. In a third subject notching in lead V₂ disappeared after cooling the chest. Inspection of the QRS complexes and measurement of the Q-Tc (V₂) showed only minor variations from the basal Q-Tc. The ST segments in leads V₂, V₃, and V₄ were raised in 11 subjects and, with the exception of 2 subjects, showed bowing with an upward concavity. In every instance the U wave remained unaltered.

When the abdomen or thigh was cooled

(control), no electrocardiographic changes were observed.

Plasma Potassium

The average basal plasma potassium was 4.74 (S.D. 0.28) mEq./L. prior to precordial cooling (experimental group) and 4.72 (S.D. 0.21) mEq./L. prior to abdominal or thigh cooling (control group). In figure 2a the serial decrements of the plasma potassium are shown for both groups. There was a relatively marked progressive decrease of plasma potassium in the experimental group (−0.39 mEq./L. at 60 minutes) as compared with the small decrease in the case of the control group (−0.10 mEq./L. at 60 minutes). Application of the t test showed that the difference was highly significant (fig. 2a). An hour after precordial cooling, the plasma potassium approximated the basal value.

The 2 ethnic groups showed similar responses but not all individuals reacted according to the pattern outlined above. A significant decrease of plasma potassium was taken as $3 \times \text{S.D.}$ of the error of the estimation ($3 \times 0.086 \text{ mEq./L.}$). According to this criterion, 1 African subject showed an insignificant deviation on precordial cooling. A relatively marked drop in plasma potassium concentration occurred in 2 subjects with abdominal or thigh cooling. In one of these a maximum drop of 0.31 mEq./L. occurred at 45 minutes and persisted to the end of the recovery period; this drop however was not as great as that reached with precordial cooling, viz., 0.51 mEq./L. In the other subject a maximum decrease of 0.36 mEq./L. was found at the 30- and 60-minute intervals with recovery above the basal value an hour later; here again the decrease after cooling the chest was greater, i.e., 0.49 mEq./L. In general, however, the results clearly demonstrated that a decrease of plasma potassium was induced specifically by precordial cooling.

Relation Between T Wave and Potassium Changes

A parallel drop in the T wave and plasma potassium is illustrated by the mean decrements depicted in figure 2a and 2b. The decre-

TABLE 2.—Average Alterations (Compared with the Basal Values) of the Pulse Rate, Blood Pressure, and Skin Temperature

	Pulse per min.		B.P. mm. Hg		Skin temperature (ankle) °C.	
	60-min. cooling	Recovery	Maximal change 15-60 min. cooling	Recovery	60-min. cooling	Recovery
European						
Chest.....	-3.9	-3.1	+4.6 +6.2 +3.6 +6.6	+0.6 +2.6 +6.0 +3.6	-1.0	-0.8
Control.....	+0.2	-0.5			-1.3	-1.3
African						
Chest.....	-7.6	-6.1	+6.2 +11.0 +4.0 +5.0	+3.2 +6.0 +1.0 +5.2	-1.7	-2.3
Control.....	-2.1	-2.8			-1.9	-2.4

ments were however uncorrelated. The correlation coefficient between the decrements of the T-wave amplitude and the decrease of plasma potassium was calculated for the data at the 60-minute time interval. The variables taken were the percentage deviations from the basal values. For these data $r = +0.381$ ($t = 1.75$, D.F. = 18, $p > 0.10$), which represent an insignificant correlation. In addition, there were exceptional cases. Firstly, with precordial cooling the one African student whose electrocardiogram did not change showed a drop in the potassium (-0.46 mEq./L.); secondly, the reverse occurred in another African; and thirdly, in the control studies 2 subjects showed a drop in the plasma potassium on abdominal or thigh cooling without any alterations in the electrocardiogram.

Other Investigations

The decrease in the plasma potassium concentration could not be accounted for by any change in the plasma volume (calculated according to the formula $\frac{PV_2}{PV_1} = \frac{Hb_1}{Hb_2} \times \frac{1 - Ht_2}{1 - Ht_1} \times 100$ where PV = plasma volume, Hb = hemoglobin in Gm./100 ml., Ht = hematocrit) nor by an excess excretion of potas-

sium in the urine. No significant modifications in the plasma sodium and calcium were obtained.

The precordial cooling was accompanied by a reduction in the pulse rate. The blood pressure rose, the diastolic more than the systolic, and the skin temperature over the ankle dropped with cooling of the chest and of the abdomen or thigh. All these alterations (table 2) were more marked in the African group.

The eosinophil counts and the levels of blood glucose did not indicate that cooling elicited an adrenal response. These findings do not necessarily rule out an adrenocortical response selectively affecting the plasma potassium level.

DISCUSSION

The progressive depression and inversion of the T waves in leads V_1 to V_4 are theoretically due to delayed repolarization of the anterior surface of the ventricles, lying adjacent to the recording electrodes. Similarly, the notching of an otherwise smooth descending limb of the T wave would be compatible with a disparity in the rate of the repolarization between portions of the myocardium. The findings in the limb leads are also consistent with involvement of the anterior surface of the heart. The assumption is made, therefore, that these manifestations were due to cooling of the anterior surface of the myocardium as a result of penetration of cold through the chest wall. The analogous responses of the electrocardiogram obtained in experimental animals, in which the hearts were cooled directly, support this hypothesis. The direct correlation between experimentally produced temperature changes of the heart in dogs and the concomitant alterations in the voltage of the T wave¹⁴ also favors this supposition.

The exaggerated response of the electrocardiogram in the African could therefore be attributed to a greater degree of cooling of portions of the epicardial surface. Certain factors would appear to facilitate the conduction of the cold through the chest wall to the heart in the African. Firstly, the African students had a relatively thin skin fold over the precordium. Taken in conjunction with

the lower average weight of the African compared with the European group, the possibility exists that the heart in the African is not as well insulated by subcutaneous and possibly also by deep fat. Indeed, Rahman and co-workers⁶ noted that in poorly nourished subjects the electrocardiographic response to precordial cooling was greater than in well nourished individuals. The observations of Piaggio Blanco and associates³ are also relevant; they obtained the most marked modifications in the T wave in a subject with a rib resection whose heart was close to the skin; conversely, the least alterations in the T wave were seen in subjects with pneumothorax or emphysematous bullae, where the air acted as a poor conductor between the icebag and the heart.

Secondly, measurements of the circumference and anteroposterior diameters between bony points at various levels revealed that the chest was smaller in the African than in the European. Thus, in the smaller thoracic cage of the African the heart may be close to the anterior chest wall; consequently the heart would be more readily cooled by an icebag on the precordium. While the precordial thickness of fat and size of the chest may contribute to the differences in the response of the electrocardiogram in the 2 ethnic groups, there were a number of exceptions. A comparative study on a larger scale of the orientation and insulation of the heart in the 2 ethnic groups may provide evidence to confirm the postulates made. Whether there is a relationship between this readily producible inversion of the precordial T waves in the African and the so-called spontaneous inversion in Africans^{5, 15} and American Negroes,^{16, 17} requires consideration.

The cooling of the myocardium was also probably responsible for the slowing of the heart rate (table 2). However, it is unlikely that the heart was cooled sufficiently (the precordial skin temperature having been decreased by 18 C.) to produce an "injury potential" of the myocardium. The possibility may be entertained that the raised ST segment, found in 11 subjects, could be due to the slowing of the recovery process resulting in a "con-

tinuum of the potential imbalance from one cycle to another."¹⁸

The mechanisms whereby cold retards the rate of repolarization remains to be explained. Coronary vasospasm with consequent diminution in blood supply is a suggested mechanism.⁸ A vagotonic response to cold, which is alleged to be exaggerated in the African (Bantu), has been implicated.⁵ The present investigation does not permit an assessment of these possibilities.

Current theory holds that the ionic transfer, particularly of sodium and potassium, across the membrane is related to the potential changes in nerve and muscle.¹⁹ The relationship of the plasma potassium concentration to the T wave has been comprehensively reviewed.^{20, 21} In the present experiment it was demonstrated that the plasma potassium concentration and the height of the T wave decreased progressively in a parallel fashion (fig. 2). Whether these 2 variables are mutually dependent or are independent manifestations of precordial cooling cannot easily be assessed. Presumably, the drop in the plasma potassium level was a parameter of an altered intracellular and extracellular potassium balance in the cardiac muscle, modifying the T wave. Admittedly, there was a lack of correlation between the decrements of the concentration of plasma potassium and the amplitude of the T wave. But the plasma potassium level per se is no indication of the intracellular and extracellular equilibrium of potassium in the heart. Furthermore, the individual sensitivity of the heart to a decrease in the plasma potassium must also be taken into account.

The mechanism whereby precordial cooling lowers the plasma potassium remains to be established. The decrease in the concentration cannot be accounted for by hemodilution or increased urinary excretion. While further blood volume studies and more urinary estimations are necessary to confirm these results, it is to be inferred at present that a change in the intracellular-extracellular potassium balance has occurred. It is unlikely that the heart alone retained the amount of potassium lost from the extracellular compartment. The average maximum decrease in the plasma

potassium of the subjects investigated was 0.20 mEq./L.; if an extracellular fluid volume of 20 per cent of the body weight is assumed, the loss from the extracellular compartment for these subjects can be calculated as 5 to 6 mEq. Since the heart contains approximately 25 mEq. of potassium,²² it would have meant an extremely high proportion of potassium uptake by the cardiac muscle alone. An increased uptake of potassium by the heart would indeed be contrary to the findings reported on generalized hypothermia of an increased output of potassium by the heart.²³ Furthermore, it has been shown that cooling of isolated striated muscle (rat diaphragm) produces a decrease in the rate of inflow of potassium into the muscle.²⁴ In our control experiments cooling of striated muscle (abdominal and thigh) did not generally alter the plasma potassium concentration.

From the available literature, no information was obtained about the movements of electrolytes during local cooling of the heart in the intact animal or in man. During generalized hypothermia, however, a rise in the potassium has been reported in rats,²⁵ dogs,^{26, 27} and unanesthetized human subjects.²⁸ On the other hand, a fall in the potassium has also been obtained in dogs.^{27, 29, 30} The rise in the plasma potassium in the case of the cooled rats was attributed to shivering and an associated, increased liver glycolysis. Shivering could also have accounted for the rise in plasma potassium in the human subjects. The cause for the fall in the plasma potassium in dogs was considered in terms of a rise in pH produced by hyperventilation, but a decrease in the plasma potassium was also obtained.²⁹ The carbon dioxide content of the blood could not be correlated with the changes in the plasma potassium.²⁷ In our experiments, shivering did not occur nor were there any obvious changes in the rate and depth of respiration. Hence these complications did not disturb the plasma potassium level.

As the modifications, both in the electrocardiogram and in the level of the plasma, were detected only with cooling of the chest, it is tempting to ascribe the cause of these modifications to a common factor. In general terms it may be postulated that the cold inhibited a

chemical system in the myocardium concerned with the ionic exchange related to the repolarization process. Disturbance of this system may have triggered a reaction affecting the potassium transfer from the extracellular to the intracellular compartment. Perhaps the affected system involved the acetylcholine-cholinesterase relationship to the potassium and the repolarization process.³¹ While it is well known that potassium profoundly affects cardiac activity, the results of our experiments suggest that a decrease in temperature of the heart may in turn affect potassium metabolism in general.

SUMMARY

Cooling of the anterior chest wall in 20 students (10 African and 10 European) resulted in depression and inversion of the T wave in leads V_1 to V_4 and a concomitant decrease in the plasma potassium concentration. The most marked T-wave modifications occurred in African students and this has been attributed to a greater penetration of cold to the myocardium.

From investigations of the urinary potassium excretion and from calculations of the plasma volume it has been inferred that the decrease of the plasma potassium concentration was due to a passage of potassium into the intracellular compartment.

As the T-wave modifications and the decrease of the plasma potassium concentration occurred specifically with cooling of the chest wall and not when other localized areas of the body were cooled, it is postulated that cooling of the heart affected a mechanism that influenced both the repolarization process and the regulation of potassium metabolism.

ACKNOWLEDGMENT

We wish to thank Professor Joseph Gillman, Dr. S. Brenner, and Dr. B. van Lingen for helpful criticism and advice during the preparation of this paper. We are grateful to those students of the 1953 physiology class for volunteering as experimental subjects. Thanks are due to the University Research Committee for a grant to one of us (B. K.) to purchase a Sanborn electrocardiograph.

SUMMARIO IN INTERLINGUA

Frigidation del pariete antero-thoracic in 20 studentes (10 african, 10 europeae) resultava

in le depression e inversion del unda T in le derivationes V_1 a V_4 e un reduction concomitante in le concentration del kalium plasmatic. Le plus marcate modificationes del unda T occurreva in studentes african, un facto attribuite al plus profunde penetration del frido usque al myocardio.

Super le base de investigationes del excretion urinari de kalium e de calculationes del volumine plasmatic il ha essite possibile concluder que le reduction del concentration de kalium in le plasma esseva le resultado de un passage de kalium a in le compartimentos intracellular.

Proque le modificationes del unda T e le reduction del concentration de kalium in le plasma occurreva specificamente post frigidation del pariete thoracic e non quando altere areas localisate del corpore esseva frigidate, il es possibile postular que le frigidation del corde afficeva un mecanismo que influentiava tanto le processo de repolarisation e le regulation del metabolismo de kalium.

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Hypotensive agents were administered to a series of patients, some hospitalized, some ambulatory, with hypertensive disease of all degrees of severity. Dosages were such as to produce either apparent lowering of blood pressure or undesirable side effects. Hydralazine, hexamethonium, rauwolfia, veratrum alkaloids, and the low-sodium diet were used. It is pointed out that the usual method of evaluation fails to give an accurate picture of the specific role of these drugs in a treatment regimen. Data indicated that (1) inclusion of a patient in a special study may exert a hypotensive effect; (2) medicaments exert an additional effect (controlled by placebo-drug alternation); (3) nonpharmacologic stimuli in the experimental situation may have equal effect to the drug. The appraisal method outlined is of critical importance in the study of specific effects of hypotensive drugs. Of the drugs that were tried, none was found to have a specific role in treatment of hypertensive disease.

KITCHELL

Interatrial-Pressure Relationships after Closure of Atrial Septal Defects in Man

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Manifestations of left ventricular failure have been reported in the literature in some patients after surgical closure of atrial septal defects. The authors present their experience in their series of 85 cases and detailed hemodynamic measures in 16 patients.

RECENTLY Watkins and Gross¹ described a clinical syndrome that followed surgical closure of atrial septal defects in some of their patients. This syndrome consisted of the retention of fluid and a gain in weight during the early postoperative period. At times there followed tenderness in the right upper quadrant of the abdomen, hepatomegaly, and roentgenographic evidence of pulmonary congestion and enlargement of the left atrium. They attributed this syndrome to transient left ventricular failure resulting from the increased work load imposed on the left ventricle by the correction of the left-to-right shunt through the atrial septal defect. Hickler and Goodale² described a fall in the right ventricular and a rise in the left atrial or pulmonary artery wedge pressure accompanied by an increase in the left ventricular stroke work after closure of atrial septal defects; these studies suggest the hemodynamic potentials for the subsequent development of left ventricular failure.

Left ventricular failure following closure of an atrial septal defect has been recognized clinically in only 1 of the series of 85 patients operated on by the atrial-well technic at the Mayo Clinic. This series was therefore reviewed in order to determine whether certain physiologic data, obtained during operation, might clarify the hemodynamic response of the heart to closure of the atrial septal defect. From the total group were selected all cases in which sufficient hemodynamic data had been obtained for evaluation of left and right atrial pressure changes effected by closure of the atrial septal

defect. There were 16 such cases and they form the basis for this report.

MATERIAL AND METHODS

Information on preoperative pressure relationships between the atria was available from the data obtained during cardiac catheterization. The procedure and the recording systems used have been described previously.^{3,4} In some instances the cardiac catheter passed through the atrial septal defect so that a direct determination of left atrial pressure was obtained, this being followed within a short time by a determination of right atrial pressure on withdrawal of the catheter. Where left atrial pressure was not determined, the pulmonary artery wedge pressure was used as representative of it.⁵ The time interval between the recording of right atrial pressure and the recording of pulmonary artery wedge pressure varied considerably.

Pressures were determined during operation before and after closure of the atrial septal defect; the recording systems used have been described elsewhere.⁶ Continuous monitoring of the central venous or right atrial pressure was obtained by inserting a plastic catheter by way of a peripheral vein into the superior vena cava or right atrium. Right ventricular pressure was determined by means of a plastic catheter introduced into the right atrium through the atrial well and advanced into the right ventricle. After closure of the atrial septal defect and removal of the atrial well, left atrial and right atrial pressures were recorded by means of a 22-gauge needle inserted through the atrial wall.

The photokymographic records obtained during operation were reviewed. Mean pressures were determined by planimetric integration over at least 1 respiratory cycle. Most records of simultaneous atrial pressures contained simultaneous "flush" calibrations on both manometric systems during the actual recording so that a high degree of accuracy in measurement of differences in pressure between the 2 atria was attained.

For the purpose of this study, the interatrial gradients recorded in the results are the pressures in millimeters of mercury by which the left atrial pressure exceeded that in the right atrium, and are

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recorded as negative when right atrial pressure exceeded left atrial pressure.

CLINICAL DATA

The youngest patient in this group was 11 and the oldest 48 years of age, the average age being 27 years. There were 13 females and 3 males. Four patients presented a history compatible with at least 1 episode of frank cardiac failure. Four patients, on the other hand, were entirely asymptomatic. In addition to the atrial septal defect, patient 13 was thought clinically to have possible mitral stenosis on the basis of a definite history of rheumatic fever as a child and the presence of an apical diastolic murmur. Patient 10 also had an apical diastolic murmur.

RESULTS

Table 1 is a summary of the pertinent clinical data, the surgical findings, and the postoperative course in the 16 cases. All patients survived. The results of the dye-dilution studies carried out after closure of the defect are included.

Surgical Findings. In 14 of the 16 cases repair of an isolated atrial septal defect was accomplished with the atrial-well technic of Gross.⁷

In 1 case (case 5) a closed technic was utilized to repair an atrial septal defect and to correct an anomalous pulmonary venous connection from the right upper lobe to the superior vena cava. An interatrial communication of the partial persistent common atrioventricular canal type was found in case 16. A prosthesis of polyvinyl formal (Ivalon) sponge was used to close the defect in all cases in which the well was employed. As seen from table 1, the size of the defect, as estimated by the surgeon, varied from 3 by 2.5 cm. to 7 by 5 cm., the average being 4.5 by 3 cm.

Additional surgical findings included mild tricuspid regurgitation in 3 cases and mild mitral regurgitation in 1. Examination of the mitral valve in cases 10 and 13 revealed an orifice that seemed narrowed although the leaflets were normal to palpation. The valve was digitally dilated prior to closure of the atrial septal defect in case 10.

Results of Closure. Indicator-dilution curves obtained by use of Evans blue dye, except for showing prolongation in all time components

TABLE 1.—Clinical and Surgical Data in Cases of Atrial Septal Defect

Case	Age, sex	N. Y. heart classification	History of cardiac failure	Surgical findings	Mitral valve*	Tricuspid valve*	Estimated size of defect, cm.	Dye curve after closure	Postoperative complication
1	13 M	I-A	—	ASD	N	N	5 x 3	Normal	None
2	27 F	I-A	—	ASD	N	N	6 x 4	Sl. L-R	None
3	11 F	II-B	—	ASD	N	N	4 x 2	Normal	None
4	45 F	II-B	—	ASD	N	N	4 x 3.5	Normal	None
5†	23 F	II-B	Yes	ASD and APVC‡	N	N	4 x 3	Normal	None
6	48 F	II-B	Yes	ASD	N	R	4 x 3	Normal	Atrial fib.
7	19 F	I-A	—	ASD	N	N	4 x 2	Normal	None
8	31 F	II-B	—	ASD	N	N	5 x 3	Normal	Tachycard.
9	23 F	I-A	—	ASD	N	N	5 x 4	Normal	Atrial flut.
10	23 F	II-B	—	ASD	§	N	7 x 5	Sl. L-R	Tachycard.
11	18 F	II-B	—	ASD	N	N	5 x 3	Normal	Atrial flut.
12	14 F	I-A	—	ASD	N	N	3.5 x 2.5	Normal	None
13	34 F	II-C	Yes	ASD		N	4.5 x 3	Normal	Empyema
14	44 M	II-C	Yes	ASD	N	R	3 x 2.5	Normal	Tachycard.
15	32 M	II-B	—	ASD	N	N	5 x 4	Normal	Tachycard.
16	25 F	II-B	—	AVC¶	R	R	5 x 3	20% L-R	None

* N = normal, R = mild regurgitation.

† Repaired by closed technic.

‡ Anomalous pulmonary venous connection from right upper lobe to superior vena cava.

§ Mitral valve ring narrow to palpation. Digitally dilated.

|| History of rheumatic fever as child. Many episodes of failure. Diastolic murmur at apex. Mitral valve ring narrow at operation.

¶ Partial persistent common atrioventricular canal.

TABLE 2.—Preoperative Left and Right Atrial Pressures (mm. Hg) and Related Data

Case	Right atrium			Left atrium or pulm. art. wedge			Left minus right atrial pressure, mean gradient	L-R shunt,* (per cent)	Cardiac ind., L./min./M. ²
	Max.	Min.	Mean	Max.	Min.	Mean			
1	5	1	3	15	5	8	5	60	5.2
2	6	1	4	8	3	6†	2	58	4.4
3	1	-2	0	4	0	3†	3	47	3.6
4‡	4	-1	2	—	—	—	—	—	2.6
5	7	2	5	9	4	7	2	50	3.5
6‡	6	0	4	—	—	—	—	—	2.2
7	9	4	6	13	7	10	4	78	3.1
8	7	2	4	10	1	5†	1	42	5.2
9	9	4	7	15	8	11	4	65	3.9
10	10	3	6	12	9	10	4	78	2.8
12	4	1	3	7	3	5	2	57	3.5
13	5	0	3	14	10	11	8	72	2.8
14	7	2	5	8	5	7†	2	36	2.2
15	10	5	7	15	9	11	4	63	2.5
16	7	2	5	13	5	9	4	76	3.3
Average.....	7	2	4	11	5	8	3.5	60	3.4

* Left-to-right shunt via atrial septal defect expressed as per cent of pulmonary blood flow.

† Directly recorded left atrial pressure.

‡ Pulmonary artery wedge pressure or left atrial pressure or both not obtained.

TABLE 3.—Left and Right Atrial Pressures (mm. Hg) Recorded During Operation after Closure of Atrial Septal Defect

Case	Right atrium			Left atrium			Left minus right atrial pressure, mean gradient
	Max.	Min.	Mean	Max.	Min.	Mean	
1	7	4	5	13	4	9	4
2	5	2	4	4	1	3	-1
3	8	3	5	13	8	10	5
4	7	3	5	11	5	8	3
5	9	4	6	12	5	9	3
6	13	8	11	14	9	12	1
7	9	6	8	14	8	11	3
8	3	0	1	7	-3	1	0
9	4	1	3	10	3	7	4
10	1	-2	0	14	6	10	10
11	11	7	9	15	8	12	3
12	6	3	5	9	3	6	1
13	8	3	6	32	13	24	18
14	12	8	10	12	8	10	0
15	3	0	2	11	3	7	5
16	8	3	5	11	3	7	2
Average.....	7	3	5	13	5	9	4

in some cases, were interpreted as normal in 13 cases following closure of the atrial septal defect. In 2 cases there was evidence of a very small residual left-to-right shunt, and in 1 case (case 16, common atrioventricular canal) there

was a residual left-to-right shunt estimated to be about 20 per cent. Later postoperative cardiac catheterization in this case indicated the shunt to be at ventricular level.

Hemodynamic Data. The preoperative non-simultaneous left and right atrial pressures are compared in table 2. Included are the estimated left-to-right shunts, as calculated from the oxygen saturation data available, and the systemic output expressed as the cardiac index (liters per minute per square meter of body surface).

Preoperative data were incomplete in 3 cases. In the remaining 13 cases there was a positive mean interatrial gradient ranging from 1 to 8 mm. Hg, the average being 3.5 mm. This average gradient is similar to the gradients across atrial septal defects reported by others^{2, 8, 9} and is within the range of interatrial gradients found in cardiovascular normals.^{10, 11} The left-to-right shunt in these 13 cases varied from 36 to 78 per cent, the average being 60 per cent. The systemic output was essentially within normal range in these cases, in accordance with what has usually been found in a large series of cases studied in this laboratory.¹²

Table 3 gives a comparison of the atrial pres-

TABLE 4.—Mean Right Atrial Pressures (mm. Hg) Recorded During Operation before and after Closure of Atrial Septal Defect

Case	Before closure	After closure	Change (decrease)
1	9	5	4
2	9	4	5
3	7	5	2
4	8	5	3
5	7	6	1
6	11	11	0
7	12	8	4
8	4	1	3
9	11	3	8
10	11	0	11
11	10	9	1
12	8	5	3
13	11	6	5
14	12	10	2
15	11	2	9
16	9	5	4
Average	9	5	4

tures recorded after closure of the atrial septal defect in the 16 cases. It can be seen that a positive mean interatrial gradient was present in 13 cases. This gradient was unusually high in 2 of the 13 cases (cases 10 and 13), although in only 1 of these (case 13) was an abnormally high left atrial mean pressure demonstrated. In 2 cases mean atrial pressures were the same, and in 1 there was a negative interatrial gradient. The average of 4 mm. Hg for the mean interatrial gradients is not greatly different from the corresponding average of 3.5 mm. obtained preoperatively.

Inspection of table 4, which compares right atrial pressures obtained during operation before closure and prior to application of the atrial well with those obtained after closure and after removal of the well, reveals a fall in the mean right atrial pressure in 15 of the 16 cases. Interpretation of these changes without precise knowledge of the blood volume at the time of the measurements is difficult. In practically all cases in this group the right atrial pressure was higher during thoracotomy prior to opening the atrial well than it was during preoperative cardiac catheterization.

Left atrial pressures were not obtained during operation before closure of the atrial septal

TABLE 5.—Mean Left Atrial Pressures (mm. Hg) before and after Closure of Atrial Septal Defect

Case	Left atrium before operation	Right atrium before closure	Left atrium after closure	Change in left atrial pressure*
1	8	9	9	+1
2	6	9	3	-3
3	3	7	10	+7
4†		8		
5	7	7	9	+2
6†		11		
7	10	12	11	+1
8	5	4	1	-4
9	11	11	7	-4
10	10	11	10	0
11†		10		
12	5	8	6	+1
13	11	11	24	+13
14	7	12	10	+3
15	11	11	7	-4
16	9	9	7	-2
Average	8	9	9	+1

* Increase of pressure in left atrium after closure of defect as compared with pressure before operation is indicated by a plus (+) sign, decrease by a minus (-) sign.

† No preoperative left atrial or wedge pressures available.

defect for direct comparison with those obtained after closure. However, since all the defects were large (estimated area of minimal defect: 7.5 cm.²), it can be assumed that before closure the mean left atrial pressures were similar to mean right atrial pressures recorded at this time. There was no consistent difference between the mean left atrial pressure after closure of the defect and the right atrial pressure prior to closure or the left atrial pressure recorded preoperatively (table 5).

In 13 cases in which data on changes in right ventricular pressure effected by closure of atrial septal defect were available for comparison, the right ventricular systolic pressure remained unchanged after repair in 1, it increased in 3, and it decreased in 9. The over-all average change was a decrease of 9 mm. Hg.

DISCUSSION

Transient left ventricular failure was not recognized clinically during the postoperative

period in any of the 16 cases for which physiologic data before and after surgery are presented. In 2 of the 16 cases an abnormally high interatrial gradient was demonstrated after closure of the atrial septal defect, but in only 1 of these cases was the left atrial pressure elevated. In both of these cases it was thought at operation that there was narrowing of the mitral valve ring, to which the high interatrial gradients might be related. From the pressure data available, it seems apparent that the left side of the heart is immediately able to adjust to the closure of an atrial septal defect without an abnormal increase in left atrial pressure. Moreover, in 5 of the 16 cases in which right atrial and pulmonary artery wedge pressures were determined at cardiac catheterization done from 14 days to several months after closure of the atrial septal defect, there were no elevations of mean wedge pressure and no interatrial gradients of more than 5 mm. Hg. Hemodynamically, these patients are completely normal.

It may be that, if pressure data during operation had been available in some of the cases in the older age groups, elevations of left atrial pressure suggesting hemodynamic left ventricular failure might have been observed. Indeed, the 1 patient (not among the 16 cases of this study) in whom clinical evidence of temporary left ventricular failure developed after closure of an atrial septal defect was an older woman in whom, unfortunately, no physiologic studies were carried out during operation. The essential features of this case are as follows.

The patient, a woman 60 years old, had tolerated her defect with surprisingly few symptoms until 1 year before admission, at which time she began to present clinical evidence of cardiac decompensation for which she received digitalis. Pertinent findings on examination at the clinic included systemic hypertension, a grade II pulmonary systolic murmur and an increased pulmonic second sound, a grade II apical systolic murmur, and an enlarged, tender liver. An electrocardiogram revealed partial right bundle-branch block without evidence of left ventricular hypertrophy. A roentgenogram of the thorax was interpreted as showing cardiac enlargement, including enlargement of the left atrium and increased pulmonary vascular markings. Clinically

it was thought that the patient had mitral insufficiency in addition to an atrial septal defect.

At cardiac catheterization the pressure in the right atrium was 14/7, with a mean of 11 mm. Hg, and the pulmonary artery wedge pressure was 26/13, with a mean of 16 mm. Thus, although the mean interatrial gradient was only 5 mm., both atrial pressures were elevated. Pressure in the radial artery measured 190 mm. Hg systolic and 102 diastolic. The left-to-right shunt as calculated from the saturation data was 60 per cent.

At operation the left atrium and pulmonary veins were unusually large, and mitral insufficiency was noted on digital exploration through the defect in the atrial septum. Repair of this defect, which measured 2.5 by 2 cm., was accomplished in the usual manner by means of the atrial-well technic and a prosthesis of polyvinyl formal (Ivalon) sponge. It was considered that an excellent closure had been obtained.

During the first 7 postoperative days convalescence was uneventful except for evidence of slight gain in weight. On the seventh postoperative day, however, severe dyspnea and orthopnea developed. X-ray examination of the thorax revealed some increase in the vascular markings of the lungs and pleural effusion on the right side. The patient subsequently improved following treatment for congestive heart failure, although open drainage was later required for empyema that developed in the right pleural space. She has been entirely free of symptoms since recovery from this somewhat complicated postoperative course.

It is difficult to say with certainty that in this case closure of the atrial septal defect per se precipitated left ventricular failure, as mitral insufficiency and hypertensive cardiovascular disease were present to complicate the hemodynamic response of the left side of the heart postoperatively.

The hemodynamic response of the right side of the heart, as evidenced by a reduction in pressures in the right atrium and right ventricle after closure of the atrial septal defect, confirms the observations of Hickler and Goodale and is likely related to the abolition of the diastolic overload of the right side of the heart.

SUMMARY

Analysis of hemodynamic data in 16 cases before, during, and after closure of an atrial septal defect revealed that during preoperative cardiac catheterization a positive gradient between the left atrium and the right atrium was consistently present, the mean interatrial

gradient averaging 3.5 mm. Hg. The average cardiac index for the group was normal.

Elevations of left atrial pressure immediately following closure of an uncomplicated atrial septal defect were not seen in these cases, and normal pulmonary artery wedge pressures were found in all cases in which sufficient late postoperative catheterization data were available.

Complicating narrowing of the mitral valve ring was present in 2 of the 16 cases, and in both an abnormally high interatrial gradient was recorded immediately after closure of the atrial septal defect. Postoperative left ventricular failure was not observed in these 16 cases, but it did occur in 1 other case in which an atrial septal defect was complicated by mitral insufficiency and hypertensive cardiovascular disease.

Hemodynamic and clinical left ventricular failure unequivocally related to closure of an atrial septal defect has not occurred in our experience. An essentially normal hemodynamic profile can be expected immediately after closure and during cardiac catheterization later, if complete closure of the defect has been accomplished.

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SUMMARY IN INTERLINGUA

Le analyse de datos hemodynamic obtenite in 16 casos ante, durante, e post le clauditura de un defecto del septo atrial resultava in le sequente constatationes:

Durante preoperatori catheterisation cardiac, un positive gradiente esseva regularmente presente inter le atrios sinistre e dextere. Le gradientes interatrial medie habeva un valor medie de 3,5 mm Hg. Le indice cardiac medie pro le gruppo esseva normal.

Elevationes del pression sinistro-atrial immediatamente post le clauditura de un non-complicate defecto del septo atrial non esseva observate in iste casos, e normal valores pro le pressioness a cuneo in le arteria pulmonar esseva trovate in omne le casos in que suffi-

cientemente tarde datos de catheterisation postoperatori esseva disponibile.

Le complication de un restriction del anello mitro-valvular esseva presente in 2 del 16 casos, e in ambe un anormalmente alte gradiente interatrial esseva registrate immediatamente post clauditura del defecto atrio-septal.

Postoperatori disfallimento sinistro-ventricular non esseva observate in iste 16 casos, sed illo occorreva in un altere caso in que un defecto del septo atrial esseva complicate per insufficientia mitral e hypertensive morbo cardiovascular.

Hemodynamic e clinic disfallimento sinistro-ventricular de character inequivocamente relationate a clauditura de un defecto del septo atrial non occorreva in nostre experientia. Un essentialmente normal profilo hemodynamic pote esser expectate immediatamente post le operation e plus tarde in catheterisationes cardiac, providite que un perfecte clauditura del defecto ha essite effectuate.

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Two hundred and sixty-one patients from whom group A streptococci were isolated were treated for 5 days with sulfadiazine. Two hundred and sixty-four patients with exudative pharyngitis due to group A streptococci received only nonspecific therapy. The use of sulfadiazine did not eradicate the streptococci and did not prevent rheumatic fever. The drug evidently inhibited antibody formation, so that recurrent pharyngitis in the sulfadiazine group was 3 times that in the contrast group. Sulfonamides should not be used in the treatment of acute streptococcal pharyngitis. However, it is pointed out that sulfonamides have proved of great value in prophylaxis against infection with group A streptococci and should continue to be utilized as a prophylactic measure.

KITCHELL

High Anterior Myocardial Infarction

XX. Studies on the Mechanism of Ventricular Activity

By MYRON PRINZMETAL, M.D., REXFORD KENNAMER, M.D., AND RASHID A. MASSUMI, M.D.

Out of a large series of patients with coronary artery disease 6 were selected with high anterior myocardial infarction. These cases are presented in detail and their special electrocardiographic characteristics are described. The difficulty in making the diagnosis of infarction by the usual leads and the need for special leads are pointed out.

THE most widely accepted electrocardiographic classification of myocardial infarction is that proposed by Wilson and his associates.¹ They classified myocardial infarction "on the basis of the leads in which characteristic modifications of both the QRS deflections and the T complexes appear and have been given names indicative of the parts of the ventricular wall known, or thought, to be involved." Eight types of infarction were recognized: anteroseptal, anterolateral, extensive anterior, high anterolateral, plain posterior, posterolateral, postero-inferior or posteroseptal and high posterolateral.

Another classification, based on the spatial situation of the area of body surface in which infarction Q waves are found ("Q area"), has been recently proposed by Grant and Murray.² After analysis of 115 cases of myocardial infarction, the following 5 general locations of the Q area were described: strictly anterior, anterolateral, inferior or diaphragmatic, strictly posterior, and high lateral.

The conventional 12-lead electrocardiogram explores a given number of positions on the body surface, namely, the roots of the right arm, left arm, left leg, and the 6 precordial positions. If the electrocardiographic manifestations of infarction should arise outside these positions, characteristic changes of infarction will not be reflected in the electrocardiogram.

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In an effort to explore the extent of diagnostic assistance that can be derived from the electrocardiogram, exploration of the body surface by multiple leads was systematically carried out in all patients with proved or suspected myocardial infarction during the past 1½ years.

In the majority of cases the area of infarcted changes invaded 1 or more of the standard lead positions and hence caused diagnostic changes in the standard electrocardiogram. In the remaining few this area lay outside the conventional lead positions. This presentation concerns those cases in which changes from the area of infarction were strictly high anterior, usually at the level of the first 3 intercostal spaces and extending from the right to left parasternal areas. Had the additional leads not been taken from the high anterior area, the correct diagnosis would have been missed. An attempt will be made to draw some practical conclusions from this experimental method of electrocardiographic study, and electrode positions that constitute the minimum number of leads sufficient for detection of the high anterior infarction will be suggested.

The characteristics of the normal electrocardiogram of the high anterior area based on a study of 106 normal subjects are discussed in the Appendix.

METHODS

One hundred forty-nine patients with various manifestations of coronary artery disease have been studied by means of multiple-lead electrocardiograms. Of these, 66 had clinical and electrocardiographic evidence of myocardial infarction of various types and ages. There were 6 cases of infarction considered to be high anterior that will be presented below.

Electrocardiograms

In addition to the conventional 12 leads each, 84 to 105 additional leads were taken. The lead positions were at the intersection of 7 horizontal lines and 12 to 15 vertical lines. The horizontal lines consisted of the intersections of 7 horizontal planes (passing by the sternal ends of the first 5 intercostal spaces, the epigastrium midway between the fifth intercostal space and the umbilicus, and finally the umbilicus) with the body surface. The vertical lines were drawn at the positions midsternal, V_{2-9} , spinal, V_1 , V_{4R} , V_{5R} , V_{6R} , and V_{8R} . For the sake of expedience in some cases 2 to 3 of the vertical lines, usually V_9 and V_{8R} , were omitted. Thus, the torso was explored from the first intercostal space to the umbilicus both anteriorly and posteriorly. The patients were supine except that the back leads were taken in the right lateral decubitus position. The apparatus used was a direct-writing Sanborn Viso-Cardiette at a paper speed of 25 mm. per second.

The electrocardiograms were pasted on diagrams representing an unfolded torso. One complex of each lead was affixed on the area of the diagram corresponding to the location from which the lead was taken. The various electrocardiographic inscriptions could then be studied with ease and their distributions in various regions of the body determined. From serial electrocardiograms studied in this manner valuable information was derived concern-

ing the changing nature of QRS, ST segment, and T waves in cases of infarction.

CASE REPORTS

Case 1. A 56-year-old diabetic man was admitted to the hospital on January 11, 1955, because of severe pain in the anterior chest with radiation to both shoulders for approximately 24 hours. He reported a mild, transient episode of precordial pain that had occurred 2 weeks prior to admission. The blood pressure was 150/90, pulse rate 84, leukocyte count 13,000, and sedimentation rate 14 mm. per hour (Wintrobe); temperature was normal. His blood pressure subsequent to admission dropped to 115/70. Except for another mild attack of chest pain associated with ectopic beats on the tenth day after admission the hospital course was uneventful.

Figure 1 represents the conventional and a portion of the multiple-lead electrocardiogram taken on the second hospital day. Although the conventional electrocardiogram is abnormal with upwardly convexing of the ST segments in leads V_2 , V_3 , V_4 , and aV_L associated with significant T-wave inversion in leads V_2 to V_5 and suspicious Q wave in aV_L , no definite diagnosis of myocardial infarction can be made. However, the leads taken from the high sternal area revealed unmistakable changes of acute myocardial infarction consisting of QS waves (complete loss of R) in leads from the first 3 intercostal

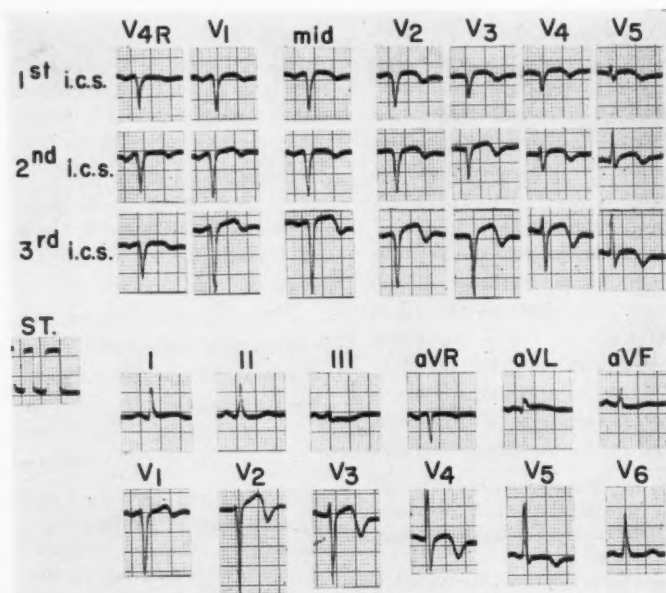


FIG. 1. Case 1. Tracing taken on second day of admission. Top 3 rows were taken from first 3 intercostal spaces. Note that QRS, ST, and T changes in V_1 , midline, V_2 , and V_3 positions are characteristic of acute infarction. In the standard limb and chest leads, however, QRS abnormalities are absent.

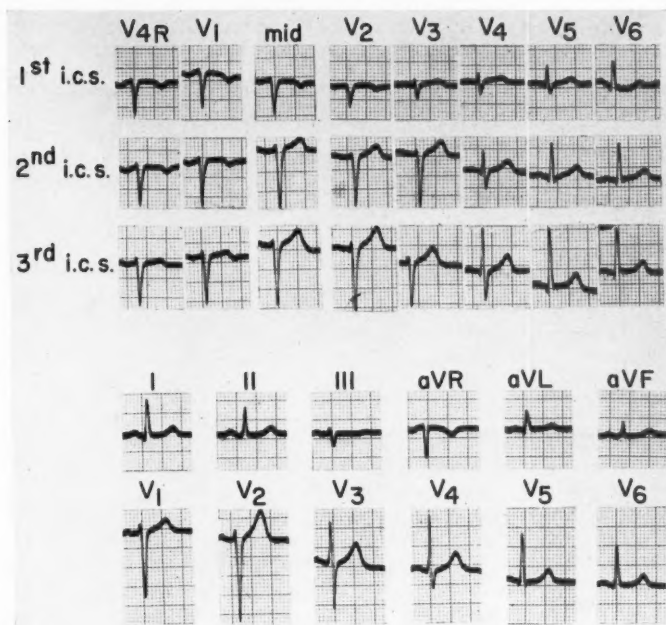


FIG. 2. Case 2. Same leads as those of figure 2 taken 11½ months after the acute attack. Note that QRS complexes in the standard limb and precordial leads remain unchanged. There is complete disappearance of the Q waves in the high sternal leads indicating the infarction nature of the initial Q waves. ST and T changes of acute stage also have disappeared.

spaces and occupying the positions V₁, midline, V₃, and V₄. In these same leads there is considerable degree of upwardly convex S-T elevation and T wave inversion rendering the QRS changes more significant.

Comment

An electrocardiogram taken on November 27, 1955, 11½ months after the attack showed complete reversal of the changes to normal (fig. 2). The S-T segment and T waves were normal and the R waves in high sternal leads, which had disappeared after the acute attack, have reappeared. This return of R indicates that the initial QRS negativity observed during the acute stage was the result of myocardial infarction. The Q area has shrunk remarkably.

The loss of the R waves in a relatively large area associated with elevation and coving of the S-T segments and symmetrical inversion of the T waves in some leads during the acute phase and complete reversal of all these alterations after recovery confirmed the clinical diagnosis of myocardial infarction. Noteworthy

is the fact that the Q area did not invade any of the conventional lead positions; the definitive diagnosis, therefore, could not have been made without additional leads. The absence of the R waves in the high sternal area cannot be explained on the basis of positional changes inasmuch as the electric axis of the heart showed no change from one record to the other. Theoretically, pronounced clockwise rotation of the heart on its longitudinal axis can cause the normal Q area to extend from its normal position in the right upper back and right shoulder to the anterior midline; such marked rotation occurs from right ventricular dilatation. In the case under discussion, however, there is no evidence of clockwise rotation. The infarction Q area is not an extension of the normal Q area because it is separated from the latter by a zone of small right chest R waves seen in leads V₁ of the third and fourth intercostal spaces and V_{4R} of the second, third, and fourth intercostal spaces in figure 1. Moreover, while the normal Q area is smooth in contour and merges subtly with the adjacent

R areas, the infarction Q area tends to be irregularly shaped and to end abruptly as in this case. Above all, the normal Q area remains constant in size; the Q area in this case decreased in size as S-T and T changes of infarction regressed.

Case 2. A 50-year-old woman was admitted to the hospital on July 18, 1954, because of anterior chest pain of 2 days' duration. The blood pressure was 135/85 and pulse 84 per minute and regular. The sedimentation rate, leukocyte count, and temperature were normal. A conventional electrocardiogram taken at this time showed symmetrical T wave inversion in leads I and aV_L without any changes in QRS or ST segment. The electrocardiogram was unremarkable otherwise.

A second conventional electrocardiogram taken on the third hospital day was identical with that of admission. On the fifth hospital day a multiple-lead record showed an area of T wave inversion beginning at the left midaxillary line and merging into the normal negative T area to the right of the sternum. The latitude of the negative T area was highest at the V_5 position, descended to the fourth intercostal space, and thence tapered off, giving the negative T area a triangular shape with the apex at the V_5 position in the fourth intercostal space and the base in the first intercostal space. Within this area the S-T segments showed up to 1 mm. elevation. Noteworthy, however, was the size of the R waves which, in an area extending from the midsternal line to V_4 position and from the first intercostal space to the third, did not increase in magnitude. This finding was considered particularly significant because these

low amplitude R waves were situated in the center of the negative T area. There was no Q area because the initial R waves did not disappear completely. Lead aV_L exhibited a normal QRS complex, isoelectric ST segment and inverted T wave.

Another multiple-lead electrocardiogram taken on the following day showed marked changes toward normal. The R waves now displayed gradual progression in magnitude toward the left, the ST segments were isoelectric and the T waves were upright (fig. 3). A third tracing taken on the eighth hospital day, following a recurrence of pain, showed only T wave inversion in this area. The tracing of the tenth hospital day was again within normal limits. Tracings taken 39 days and 15½ months after admission showed normally increasing R waves in the high anterior area, isoelectric ST segments, and upright T waves.

Comment

The serial electrocardiograms in this case showed fleeting changes involving the QRS complexes, the S-T segments, and the T waves. Although the area of T-wave inversion reached the root of the left arm and, therefore, brought about T-wave abnormality in leads I and aV_L , the area of QRS changes and S-T elevation were smaller and confined to the high anterior region of the chest. Only myocardial ischemia could have been suspected from a study of the conventional leads. However, additional leads taken from the high anterior region showed significant QRS and ST changes that warranted the diagnosis of acute myocardial infarction. The clinical picture was indicative of a relatively mild attack of myocardial infarction. The fleeting nature of the electrocardiographic changes was consistent with such a diagnosis. An interesting feature of this case was that the diminution in the size of the R wave was just as transient as the ST and T changes. This phenomenon has been observed in a few other patients with classical types of myocardial infarction in whom multiple-lead records were taken at frequent intervals.

Case 3. A 58-year-old man was admitted to the hospital on February 26, 1955, because of pain in the left chest radiating down the left arm. For 2 days prior to admission, he had had episodes of pain lasting as long as 1 hour. His blood pressure had begun to rise in 1948 and reached 190/100 early in 1955. On admission he was found to be in acute distress with chest pain. The blood pressure was 170/100. The leukocyte count was 5,300 and the sedimentation rate 1 mm. per hour. On the sixth

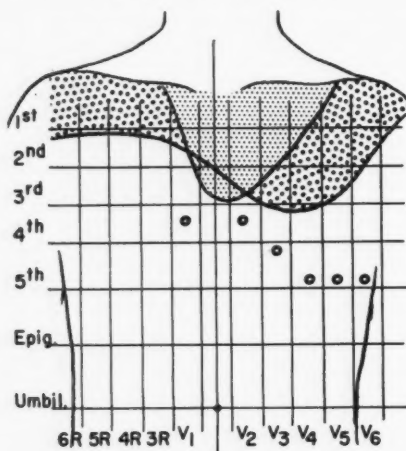


FIG. 3. Case 3. The large dotted area shows the area of T-wave inversion during the acute stage; the small dotted area depicts the area of reduced R waves. No true Q waves developed. All the changes regressed after recovery.

hospital day, the leukocyte count had risen to 9,200 and the sedimentation rate to 50 mm. per hour (Wintrobe). The blood pressure had dropped to 150/70. The leukocyte count showed further rise to 10,000 on the eighth hospital day. The serum transaminase level obtained on this day for the first time was reported as 90 U. (normal 10-40 U.).

The standard electrocardiogram taken on admission showed equivocal Q waves in aV_L and failure of the R wave to increase in amplitude from V_1 to V_4 . There was 1-mm. ST elevation in aV_L and 3- to 4-mm. elevation in leads V_1 to V_4 . The T waves were symmetrically inverted in I, aV_L , and V_2 to V_6 . There was reciprocal ST depression in leads II, III, and aV_F . This tracing showed characteristic ST-segment and T-wave changes of acute antero-septal infarction. However, the R waves did not disappear completely. The standard tracing of March 1, 1955, showed some decrease in the magnitude of ST elevation and increase in the size of the R wave in leads V_1 to V_4 .

A multiple-lead record made on March 4 showed the true extent of the electrocardiographic changes. There was a high Q area that started at the left anterior axillary line and merged into the normal Q area of right shoulder. The latitude of this Q area included the first 3 intercostal spaces at V_2 and V_3 positions and only the first 2 intercostal spaces at midline, V_1 , V_4 , and V_5 positions. Lead aV_L contained a 0.5-mm. Q wave of 0.02-second duration. There was S-T elevation ranging from 1 to 3.5 mm. in these chest leads; the T waves, however, were tall and upright.

An electrocardiogram on December 1, 1955, 9 months after the attack, showed return of the R waves in leads that had exhibited QS waves. The Q area now began on the left shoulder and extended posteriorly. The S-T segments maintained a 1- to 2-mm. elevation. The T waves remained unchanged. This electrocardiogram was consistent with left ventricular hypertrophy and strain.

Comment

The clinical picture as well as the ST elevation in the standard leads were those of acute myocardial infarction. The reduction in the size of the R waves in leads V_2 to V_4 suggested the possible proximity of these leads to infarcted myocardium; however, this was not proof of myocardial infarction for such QRS variations in the transitional zone are compatible with normalcy. No further information as to location and size of the Q area could be derived from the standard electrocardiogram.

A multiple-lead record taken on the sixth hospital day delineated the Q area and showed it to be high anterior in location. The disappearance of the Q waves and the return of the

R waves that took place after recovery from the acute attack are evidence that the Q waves were due to infarction. There was no change of the electric axis capable of explaining the QRS changes. The fact that the T waves within the Q area remained upright is explicable on the basis of the hypertensive changes that caused the T vector to rotate anteriorly, superiorly, and to the right.

Case 4. A 58-year-old woman with a history of hypertension and diabetes was admitted, on August 15, 1955, because of severe anterior chest pain of 12 hours' duration. She had had previous episodes of severe precordial pain diagnosed as "coronary insufficiency." The present attack, however, was more persistent and more intense than the previous ones. Blood pressure was at its usual level of 220/96. There was evidence of cardiomegaly and slight ankle edema. The cardiac rhythm was regular. The blood pressure dropped to 180/80 on the second day and to 150/80 on the third hospital day. The leukocyte count on admission was 10,950. Temperature ranged from 100 to 101 F. for 5 days.

The conventional electrocardiogram taken on the first day was consistent with left ventricular hypertrophy. On the second day there was ST elevation in all the precordial leads without significant T-wave changes. The QRS complexes were normal. The multiple-lead record taken on the fourth hospital day showed some ST elevation in the high precordial leads and a small Q area extending from V_1 to V_5 and present only in the first 2 intercostal spaces. The T waves in this area were upright or flat, hence not significantly different from those seen in hypertension. The conventional electrocardiogram taken at this time did not differ materially from those

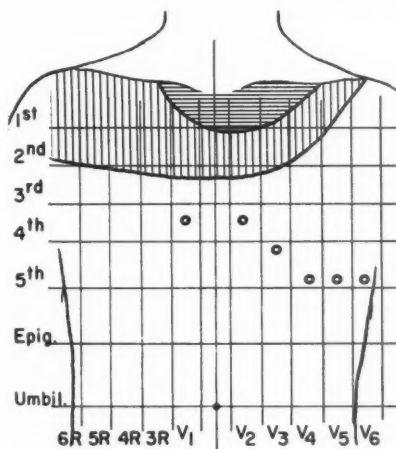


FIG. 4. Case 4. Convention. Note shrinkage of the Q area after recovery.

taken on the first 2 days. As yet there were no QRS changes. Another multiple-lead electrocardiogram taken 3 months after discharge showed complete disappearance to marked reduction in size of the Q waves in most of the leads from the high sternal area, return of the R waves, and also regression of the ST elevation (fig. 4).

Comment

The presence of myocardial injury could have been suspected from the conventional leads; however, a diagnosis of infarction could not have been made owing to failure of these leads to show QRS changes. The changes in the high sternal leads supported the diagnosis of myocardial infarction that was already suggested by the clinical picture.

Case 5. A 72-year-old man was admitted to the hospital on April 3, 1956, following a prolonged attack of precordial pain requiring opiates for relief. The blood pressure was 140/90 and pulse rate 65 and regular. The temperature was normal and remained so after admission. The laboratory tests were within normal limits. The chest x-ray revealed moderate left ventricular hypertrophy. The multiple-lead record taken on the second hospital day showed left axis deviation and T-wave inversion over the left anterolateral chest wall consistent with left ventricular hypertrophy. In the high sternal area, however, there was up to 2 mm. ST elevation followed by terminal T-wave inversion. In this same area extending from the midline to V_3 in transverse direction and from the first to third intercostal space in vertical direction the R waves appeared reduced in size. This finding, coupled with ST elevation, was considered to be evidence of myocardial infarction and the patient was treated accordingly.

Subsequent multiple-lead tracings taken on April 6, 10, 13, 16, and 20 showed gradual return of the R waves to normal size. Q waves did not appear at any time. The ST elevation receded only partially and the T waves remained unchanged. The standard limb and precordial leads failed to disclose these evolutionary changes.

Comment

In this case of clinically mild acute myocardial infarction, the standard limb and chest leads failed to show acute changes. Leads taken from the high sternal area, however, displayed evolutionary changes of the QRS and ST that, in the light of the clinical picture, were thought to be diagnostic of acute myocardial infarction. Noteworthy is the fact that QRS alterations of infarction in the high sternal leads were confined to a reduction in amplitude of the

R wave without Q waves appearing at any time. Reduction of R amplitude, occurring during the acute stage of a coronary attack, therefore may have a similar diagnostic significance to that of infarction Q wave.

Case 6. A 43-year-old man was admitted to the hospital on May 17, 1955, for cardiopericardiomy for treatment of persistent angina pectoris. He had a classical acute myocardial infarction on February 2, 1955. After discharge from the hospital he was totally incapacitated with recurrent severe anginal pain both on exertion and at rest. Physical examination revealed a blood pressure of 110/80; pulse rate of 76 per minute. Examination of the heart was not remarkable, as was the remainder of the physical examination. The serologic test was 4+ positive and the patient gave a history of syphilis.

The tracings obtained after the acute attack of February, 1955, were identical with the previous one and showed normal limb leads except for an equivocal Q wave with T-wave inversion in aV_L . There were QS waves in V_1 , QR waves in V_2 , and normal QRS complexes in V_3 to V_6 ; the ST segments in V_1 to V_4 were persistently elevated and the T waves were within normal limits. No definitive diagnosis of myocardial infarction could be made on the basis of these conventional leads. Q waves in V_1 and V_2 were of uncertain significance. A multiple-lead electrocardiogram taken on June 24, 1955, revealed a very large Q area starting around the right shoulder but extending for a considerable distance beyond its normal anterior limits and reaching the left shoulder in the transverse direction and the fourth intercostal space in the vertical direction. Small r waves, normally encountered in right chest leads, were absent.

This Q area was decidedly too large to be considered normal (fig. 5, *Left*). It could not be explained on the basis of rotation of the heart, for there was no indication of any positional changes. The S-T segments within this Q area were sharply inverted. These changes were most pronounced in high sternal leads. A diagnosis of large high anterior infarct extending over the right ventricle was made.

We had the good fortune of studying this case under direct vision after the chest was opened for the cardiac operation. After the pericardium was opened, the epicardial surface of the heart was inspected. Patchy wrinkled scars were found over the basal third of the anterior septal area and the anterior wall of the right ventricle and the basal one third to one half of the anterior surface of the left ventricle.

Direct electrocardiograms taken from the epicardial surface of the heart revealed dis-

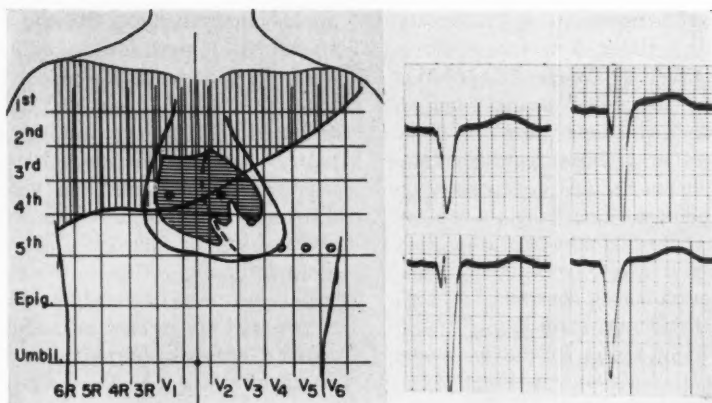


FIG. 5. Case 6. *Left*. The small striped area inside the cardiac outline is the area on the anterior aspect of the heart from which infarction Q waves were obtained. The large striped area is the Q area on body surface. Note the topographic correlation between the two Q areas. *Right*. Four various types of abnormal QRS complexes obtained directly from the infarcted region of the heart.

tinety abnormal QRS complexes in the scarred areas consisting of pure QS, QRS, and rSr' type complexes (fig. 5 *Right*). These changes were most marked over the right ventricle and the septal area. Normally, the anterior surface of the right ventricle, the septal area, and the juxtaseptal area of the left ventricle exhibit rS or RS type of depolarization complexes. The presence of scars in these areas left little doubt concerning the significance of the QRS changes.

Comment

The Q area in this case is perhaps too large to permit its inclusion in the high anterior infarct group. Actually leads V_1 and V_2 did show QRS changes of infarction. However, the main area of infarction Q waves was situated above the level of V_1 and V_2 . This case is interesting in that it demonstrates the good correlation between the Q area on the body surface and the location of infarction in the heart.* Assuming that a similar correlation existed in other patients of this group, it would be permissible to place the high anterior infarct in the basal anterior portion of the septal area and the juxtaseptal area of the ventricles.

* We wish to express our thanks to Dr. Alfred Goldman of the City of Hope Hospital, Duarte, California, for permission to take these direct leads.

DISCUSSION

With the exception of case 6, the cases described are examples of myocardial infarction of mild to moderate severity. The clinical picture in all these patients was definitely suggestive of myocardial infarction. However, a definitive electrocardiographic diagnosis could not be made from the conventional limb and chest leads because the interpretation in these cases might have been "myocardial ischemia," "coronary insufficiency," or "non-specific changes." The leads from the high sternal area substantiated the diagnosis of infarction on the basis of the following: (a) a Q area situated on and to the sides of the upper sternal region; (b) the dynamic serial changes of the QRS complexes within the Q area, including the gradual decrease in the size of the Q area associated with recovery; (c) the coexistence of the characteristic ST elevation and T-wave changes within and beyond the Q area and their return to normal after recovery; and finally (d), absence of factors such as marked positional changes or acute right ventricular dilatation to account for the QRS alterations. In cases 3 and 5 a reduction in the size of the R waves in the high sternal area made diagnosis of myocardial infarction possible. In our experience a significant loss of R potential in association with ST elevation and

T-wave inversion has proved to be of diagnostic implication. This is particularly true if reduction in R amplitude is transient, appearing during the acute phase and returning to normal in the recovery period. The significance of the reduction of the R wave in myocardial infarction has been demonstrated in experimental animals in this laboratory.³

What separates the high anterior from other varieties of anterior wall infarction, i.e., massive anterior, antero-apical, anterolateral, high anterolateral and, finally, antero-septal (often referred to as supra-apical in the European literature^{4, 5}), is the location and extent of the Q area, which to a great extent depend on the topography and size of infarction of the anterior wall. For example, the Q area of the massive anterior infarction is exceedingly large, extending from the right sternal border to left anterior axillary line and covering all the first 5 to 6 intercostal spaces. The Q area of anterolateral infarcts is large and extends laterally to the mid- and even posterior axillary line and creates typical changes in left arm leads I and aV_L. The Q area of antero-septal infarcts forms a vertical band on and to the left of the sternum and extends above and below the level of the standard V₁ and V₂ leads. In all these varieties of anterior infarction 1 or more of the conventional 12 leads fall within the Q area, hence classical changes of infarction appear in the standard electrocardiogram. In the so-called "supra-apical" infarction described by Holzman^{4, 7} and Mussafia,⁵ the conventional leads V₁, V₂, and V₃ show classical changes while the complexes of the limb leads remain normal. Electrocardiographically then, this type of infarction is very similar, if not analogous, to the antero-septal infarction. However, it is entirely possible that the "supra-apical" variety would include a proportion of the presently described high anterior infarction.

The shape of the Q varies greatly from one case to another. In 1 case of acute anterior myocardial infarction with typical QRS, ST and T changes in leads V₂, V₃, V₄, and V₅, the multiple-lead records showed the Q area to be in the form of a transverse belt extending from the midline to left anterior axillary line in the third, fourth, and fifth interspaces. The term "intermediate anterior infarction" would be

applicable to this type. Other Q areas exhibited triangular forms with the apex in the region of V₃ or V₄ and the base situated in the epigastrium or up in the infraclavicular area. The Q area of infarction does not follow any particular pattern, since the myocardial lesion itself does not. The marked individual variations in the distribution and arborization of the coronary arteries⁶ on the one hand, and alterations in the relationship of the arterial branches to various segments of the myocardium as a result of pre-existing narrowings and occlusions (so commonly found in patients with coronary arteriosclerosis) on the other, adequately explain the variability of infarction Q areas. It is important therefore to conceive of the Q area spatially and bear in mind that it can occupy any area of the body surface and be of any size and shape. This fact can be appreciated best by study of the multiple-lead records. The standard leads showing infarction Q waves, however, represent only a few selected points from the Q area. This approach is not unlike viewing an object through a few openings in its casing—an adequate knowledge of the physical characteristics of the object cannot be secured in this way.

The Q area of high anterior infarction is unique in that it is usually small and is so situated that it avoids all the standard electrode locations; hence it inscribes no Q waves in any of the conventional leads. The areas of ST elevation and T-wave inversion are usually larger than the Q area, so that in the acute stage of high anterior infarction, ST elevation and T-wave inversion may be seen in the conventional chest leads and lead I and aV_L. On the other hand, ST elevation and T-wave inversion may be found in some of the precordial and limb leads of patients exhibiting symptoms of acute myocardial infarction in whom no Q area is to be found on the body surface. We have seen 1 such case in a 46-year-old man with clinically indisputable evidence of myocardial infarction. The precordial leads V₂ to V₆ exhibited upwardly convex ST elevation of 2 to 3 mm. in amplitude and terminal inversion of the T-waves. Similar but less pronounced changes were observed in aV_L. No Q waves of infarction were found in the high sternal area or any other part of the body.

Another tracing taken 3 weeks after the acute attack showed complete disappearance of the ST and T changes. Comparison of the 2 records revealed that the R waves in the high sternal area had lost considerable amplitude during the acute stage and returned to normal after recovery. For example, R waves in leads taken from the midline at the level of the first intercostal space and from V_2 at the third intercostal space were 1.5 mm. and 5 mm. in amplitude respectively; after recovery, their respective amplitudes had risen to 2.5 and 12 mm. It will be clear, from the consideration of this case and of cases 2 and 5, that reduction in the size of the R waves within the area of ST elevation and T-wave inversion may be of great diagnostic significance. It has been found in dogs with experimentally produced myocardial infarction that the small r wave results from a mixture of live and dead epicardial muscle.³ As the infarct "heals," the number of cells of the outer myocardial layers recover and add to the height of the R wave.

A few words may be said about the retrospective diagnosis of old high anterior myocardial infarction. In our experience the electrocardiogram rapidly reverted to normal in all cases except case 6 in which a large infarction was found at operation. It may be assumed therefore that small infarcts of high anterior variety usually leave little or no residual electrocardiographic changes and hence are difficult to diagnose in retrospect. An interesting observation, however, is that, not infrequently the Q or QS waves of infarction present in the conventional precordial leads of acute anteroseptal and anterior infarcts disappear completely during the recovery period. The conventional chest leads then may appear normal. High sternal leads in such cases may disclose a Q area obviously residual to the original larger Q area.^{8, 9} In fact, Benchimol, Schlesinger, and Cotrim in 1947⁸ and Alzamora and Mispireta in 1948⁹ reported on the usefulness of high chest leads in uncovering residual QRS changes of old anterior myocardial infarcts. We have observed 2 similar cases, 1 of which showed classical acute anterior myocardial infarction with Q waves in leads V_{2-6} in March 1954. A multiple-lead record taken in 1956 shows practically normal QRS complexes

in leads V_{2-6} and a distinct Q area confined to the high sternal region. In the second case the multiple-lead record showed a relatively large Q area in the high sternal region. The standard leads V_1 to V_2 show only small r waves probably due to close proximity to the Q area. This Q area is thought to be residual of a larger Q area of a preexisting anterior infarction.

In regard to the anatomic location in the various types of anterior infarction, one may speculate that there is a fair topographic and quantitative correlation between the Q areas on the body surface and on the infarcted wall of the myocardium. All things being equal, larger Q area probably represent larger infarcts; and a Q area high in the chest corresponds to an infarction high (basal) in the heart; a Q area toward the midline would be a reflection of an infarct near or in the septal area; an "intermediate" Q area placed transversally across anterior chest wall represents an infarction of the anterior wall intermediate between base and apex, and so on. Accordingly, therefore, the type of lesion responsible for the electrocardiographic findings in this paper would be a *small* infarction located anteriorly, near the septum, and adjacent to the A-V groove. Occlusion of a *small branch* of the anterior descending coronary artery near its origin is most probably the cause. Although the assumption on which these deductions are based has not been confirmed, the available evidence¹⁰ and our own experience (case 6) give validity to such an assumption.

Clinically, the high anterior infarction runs a benign course. Those clinical features that denote a grave prognosis, namely, fever, congestive heart failure, shock, and protracted pain, have been conspicuously absent in our cases. The benignity of high anterior infarction might explain the lack of postmortem information concerning its characteristics.

The incidence of high anterior infarction cannot be inferred from the available electrocardiographic and postmortem correlation in the literature,¹⁰⁻¹² for the selection of cases in such studies would tend to exclude mild types of infarct that do not cause immediate death. Nor would it be fruitful to go over the files of hospital electrocardiograms, as here, too, high anterior infarcts would not be represented for

the same reasons. On the basis of our own experience, however, which is decidedly too limited to allow any definitive conclusions, 6 cases of high anterior infarction out of 66 electrocardiographically proved instances would suggest an incidence as high as 10 per cent of all infarcts. The occurrence of high anterior infarction may be of sufficient frequency to warrant a systematic search for it by taking additional high anterior chest leads in selected cases.

It would not be feasible to subject all patients to the multiple-lead exploration used in this study. As a routine, however, one may attempt to identify a limited number of high sternal leads in which an initial R wave is present in almost 100 per cent of normal subjects (Appendix). Then QR or QS waves or marked reduction of the R wave in such leads may signify high anterior infarction. On the basis of the study of 106 normal subjects, it seems sufficient for diagnostic purposes to record a set of only 2 high sternal leads: V_2 at the level of the second intercostal space (V_2 , 2 i.c.s.) and midline lead at the level of the third intercostal space (Mid, 3 i.c.s.). These 2 leads show an R wave in nearly 100 per cent of normal subjects, irrespective of the electric position of the heart. Like any other electrocardiographic item, the diagnostic value of a QR or QS in the above 2 leads must depend on the clinical picture and the presence or absence of other situations causing marked changes in the electric axis of the heart (right ventricular hypertrophy or dilatation, right bundle-branch block, left ventricular hypertrophy, left bundle-branch block). Elevation of the ST segments in these 2 leads were observed in all our cases of acute high anterior and other types of anterior infarct reaching the second and third intercostal spaces. Nevertheless this electrocardiographic item cannot be relied upon, for unless it is marked (Appendix), moderate ST elevation may be observed in these 2 leads in normal individuals. For a similar reason, T-wave inversion in these leads is not of diagnostic significance.

These 2 leads are useful, not only in detecting acute high anterior infarcts, but also in retrospective search for old anteroseptal and old anterior infarcts in which the Q area has re-

treated to the high sternal region. Furthermore, it is suggested that a systematic recording of the leads V_2 , 2 i.c.s., and Midline, 3 i.c.s., would allow the separation in symptomatic patients of high anterior infarction from other syndromes caused by various types of myocardial ischemia, such as angina pectoris and "coronary insufficiency," etc.

A question of general interest concerns the possible usefulness of the vectorcardiogram in the diagnosis of high anterior infarction. We have no vectorcardiograms taken during the acute stage, therefore whatever is said on the subject is purely speculative. Vectorcardiograms taken in 2 cases (case 1 and case 4) after the return of the electrocardiogram to normal were within normal limits. It is believed, on theoretical grounds alone, that vectorcardiography is unlikely to be of diagnostic assistance in this type of infarction. That portion of the QRS loop likely to show abnormality in this type of infarction would be the initial one, which is normally directed anteriorly and to the right and, depending on the electric position of the heart, may point superiorly or inferiorly. This portion of the loop is short in duration, 0.01 to 0.02 second; in still vectorcardiograms it is often buried, at least partially, in the zero point. The direction and magnitude of this portion cannot be accurately studied unless the vectors are inscribed on the moving film. In any event, total disappearance of this portion of the loop would *not* cause the loop to depart significantly from the normal. This may be one of the situations in which standard electrocardiograms may be superior to the vectorcardiograms but this problem needs complete study.

An observation of some interest made during the serial study of multiple-lead electrocardiograms in myocardial infarction was the frequency with which QRS changes of infarction were found to fluctuate within a few days. The Q areas were observed to be dynamic, enlarging in some cases and diminishing in others without necessary correlation with the clinical picture. Reduction in the size of the Q area during the first few days following the acute attack was a particularly common occurrence. Obviously shrinkage and scarring of the infarcted myocardium would not be an acceptable explana-

tion for such changes cannot occur within a few days. Instead, it would seem more logical to describe the fleeting Q waves to a state of "electrophysiologic necrosis," resulting from severe ischemic injury rather than to histologic necrosis. Since the R wave returns, the QS waves are obviously mural type QS waves as the myocardium contains viable myocardium.¹³

SUMMARY

Multiple-lead electrocardiographic exploration was carried out in 149 patients with various manifestations of coronary artery disease. Of these, 66 had myocardial infarction.

Six cases of myocardial infarction in which infarction QRS changes were absent in the conventional limb and precordial leads but were present in leads taken from the high sternal region are reported. The name "high anterior infarction" is suggested for this type so that it would be distinguished from other varieties of anterior infarction. Only some type of "myocardial ischemia" would have been recognized in routine electrocardiograms.

The diagnosis of infarction in our cases was based primarily on the characteristic clinical picture and the evolutionary changes in the QRS complexes and in S-T and T of the high sternal leads. The electrocardiograms taken from this region during the acute stage displayed QS waves, S-T elevation, and T-wave inversion. After recovery, the R waves, S-T and T reverted to normal. All these patients recovered, thus no pathologic correlation with the electrocardiographic findings is yet available. Prognosis appears to be very good.

Of interest was the observation that the QRS changes of infarction were not permanent. On the contrary, the fluctuations in the size and location of the Q area pointed to a dynamic rather than static nature of the Q waves. It was suggested that such Q waves represented mural type QS waves.

The conventional precordial leads and aV_L taken during the acute stage of high anterior infarction showed only S-T and T-wave changes. It is suggested therefore that the high sternal leads be taken in patients exhibiting symptoms of acute myocardial infarction and isolated S-T and T changes consistent with such a diagnosis in precordial and aV_L leads.

This practice may be warranted, for in our small series of 66 infarction cases, 6 instances of high anterior infarct were found.

On the basis of our study of the normal electrocardiograms taken from the high sternal area and the constancy with which an initial r wave occurs, the following 2 leads are suggested as the minimum sufficient number of leads to be taken when high anterior infarction is suspected: V_2 at the levels of the second, and midline at the third intercostal spaces. The incidence of an R in these leads is nearly 100 per cent, hence, a Q or QS in these leads in the presence of suggestive clinical symptoms would substantiate the diagnosis of acute myocardial infarction. These leads may show residual QRS changes in healed anterior and antero-septal infarcts while the standard chest leads have returned to normal.

Vectorcardiography is believed to be inferior to electrocardiography in detecting the high anterior infarction, but more study is necessary.

The systematic use of the 2 high sternal leads may be advisable in selected patients with various manifestations of coronary artery disease. This practice would serve to differentiate between cases with infarction and without infarction in otherwise undiagnosable instances.

Clinical evidence of the "mural" QS wave and the abnormally small R wave in coronary artery disease has been obtained.

SUMMARIO IN INTERLINGUA

Explorationes electrocardiographic a derivationes multiple esseva executate in 149 patientes con varie manifestationes de morbo de arteria coronari. Inter illos, 66 habeva infarimento myocardial.

Es reportate sex casos de infarimento myocardial in que alterationes infarimental de QRS esseva absente in le derivationes conventional de extremitate e precordio sed presente in derivationes ab le region supero-sternal. Le termino "infarimento alti-anterior" es proponite pro iste typo in distinction ab altere varietates de infarimento anterior. In le casos mentionate, le electrocardiographia routinari haberea revelate non plus que un typo de "ischemia myocardial."

Le diagnose de infarimento in nostre casos

esessa basate primariamente super le typic tableau clinic e le alterationes evolutionari del complexos QRS e de S-T e T in le derivationes supero-sternal. Le electrocardiogrammas derivate ab iste region durante le stadio acute exhibiva undas QS, elevation de S-T, e inversion del unda T. Post recuperation del patientes, le undas R e S-T e T retornava a configurationes normal. Omne iste patientes recuperava. Per consequente nulle correlation pathologic con le constatationes electrocardiographic pote esser establite a iste tempore. Le prognose es apparentemente multo bon.

Un observation de interesse esessa que le alterationes de QRS in infarimento non esessa permanente. Al contrario, le fluctuationes del dimensiones e del location del area Q signalava un natura dynamic plus tosto que static del undas Q. Se suggereva le notion que tal undas Q representa un typo mural de unda QS.

Le conventional derivationes precordial e le aV_1 registrate durante le stadio acute del infarimento alti-anterior exhibiva alterationes solmente de S-T e de unda T. Per consequente il es a recommendar que le derivationes supero-sternal es usate in patientes qui manifesta symptomatas de acute infarimento myocardial e isolate alterationes de S-T e T de character compatibile con ille diagnose in derivationes precordial e aV_1 . Iste practica pare justificate, viste le facto que in nostre serie de non plus que 66 casos de infarimento nos ha trovate 6 occurrentias de infarimento alti-anterior.

Super le base de nostre studio del normal electrocardiogrammas derivate ab le area supero-sternal e viste le regularitate del occurrentia de un unda r initial, le sequente duo derivationes es recommendate como le minimo sufficiente in casos de suspicion de infarimento alti-anterior: V_2 al nivello del secunde spatio intercostal e derivation de linea intermediari al tertie spatio intercostal. Le incidentia de R in iste derivationes es quasi 100 pro cento. Per consequente, un Q o QS in illos in le presentia de suspecte symptomatas clinic pote corroborar le diagnose de acute infarimento myocardial. Iste derivationes pote manifestar residuos de alterationes de QRS in curate infarimentos anterior e antorseptal post que le derivationes thoracic standard ha retornate a configurationes normal.

Nos opina que vectocardiographia es inferior a electrocardiographia in le detection de infarimento alti-anterior, sed studios additional es necessari.

Le uso systematic del 2 derivationes supero-sternal es a recommendar in seligite patientes con varie manifestationes de morbo de arteria coronari. Iste practica servirea a differenciar inter casos con e sin infarimento in situationes que escappa a altere mesuras diagnostic.

Manifestationes clinic del "mural" unda QS e del anormalmente reduce unda R in morbo de arteria coronari ha essite determinate.

APPENDIX

By RASHID A. MASSUMI, M.D.

In order to establish standards for multiple-lead electrocardiograms, 106 normotensive (blood pressure 140/90 or below) subjects without history or evidence of heart disease were studied. The electric position of the heart was classified as vertical, intermediate, or horizontal; the so-called semivertical and semihorizontal positions having been grouped together with the vertical and horizontal respectively. Table 1 represents the distribution with reference to age, sex, and blood pressure. The absence of subjects of third and fourth decades in the horizontal group is in keeping with the tendency of the electric position of the heart to shift from vertical to horizontal with advance of age. Selection of the subjects was made at random in every respect except age: an attempt was made to use as many individuals in the coronary age group (40 years and over) as possible. In the following section only those electrocardiographic items pertinent to the discussion of the high anterior infarction will be considered.

QRS Complex. The QRS complexes in the high sternal area were predominantly of the rS or rSr' type in V_1 , midline and V_2 positions and of the RS, Rs or qRs type in V_3 and V_4 positions. The transition between the rS complexes (sum negative) in the former and RS or Rs complexes (sum positive) in the latter group of leads occurred at different positions being generally farther to the left in the first than in the third intercostal space. Indeed, the position of this transition zone depended to a great extent on the electric position of the mean QRS axis being lower and more to the left in vertical hearts than in horizontal hearts. Small q waves normally seen in leads taken from the left lateral chest wall occurred in a few of the V_3 and V_4 leads. They did not exceed 1 to 2 mm. in amplitude and 0.01 to 0.02 second in duration.

The depolarization complexes in the high sternal area exhibited an initial r or R in a large majority of the subjects. Special attention was given to the initial portion of the QRS complex due to its great

TABLE 1.—*Variation of Cardiac Position with Age, Sex, and Blood Pressure*

	Mean	Decade distribution						Range	Sex		Blood pressure		Total
		3	4	5	6	7	8		M	F	Systolic	Diastolic	
Vertical.....	41.2	4	13	20	6	1	0	21-66	26	18	140-100	90-60	44
Intermediate.....	48.3	3	3	22	13	2	1	21-74	24	20	140-105	90-64	44
Horizontal.....	48.3	0	0	11	6	1	0	41-60	14	4	140-110	90-68	18
Total.....													106

importance in the diagnosis of myocardial infarction. Q waves were uncommon in the high anterior leads occurring in the entire population of our sample (106 cases) with the following per cent frequencies: in the first intercostal space, V_1 , 8.8; Midline, 10.3; V_2 , 1.9; V_3 , 0.9; V_4 , 0; in the second intercostal space, V_1 , 4.3; Midline, 1.9; V_2 , 0.9; V_3 , 0; V_4 , 0; in the third intercostal space, V_1 to V_4 , 0. Thus the only leads that show initial Q with a significant frequency are V_1 and midline in the first intercostal space and V_1 in the second intercostal space. Lead V_2 in the second intercostal space displayed a Q wave in only 1 case out of 106 (0.9 per cent). Leads V_3 and V_4 of the same space, and all the 5 leads in the third space showed no Q waves; the depolarization complexes began with an initial positivity. A breakdown of these frequencies according to the electric position of the heart may be found in tables 2, 3, and 4.

Statistical analysis of the data revealed no significant differences in the frequencies of the occurrence of Q waves when corresponding leads in the 3 groups of hearts were compared. Therefore, with certain reservations owing to the small size of our samples, the presence or absence of a Q in high sternal leads does not seem to be a function of the electric position of the heart. We are not in a position to speculate on the possible explanations for the variations in the initial portion of the QRS complexes. Attempts to correlate the distribution of the initial Q with age and body habitus failed to provide any clue.

The amplitude and duration of the initial r waves of the high sternal leads were found to vary markedly. Tables 2, 3, and 4 depict the mean, standard deviation, the mode (that value occurring most frequently), and the range for the amplitude and durations. It may be noted, from the relatively larger standard deviations and ranges for the amplitudes than for the durations, that the former display greater scatter than the latter. This is consistent with the greater variations seen in the amplitude of the entire QRS complexes than in their duration. Noteworthy in these tables is that intergroup variations of the amplitudes and durations are negligible. Stated differently, the amplitudes and durations of the initial r waves in the high sternal leads (all 15 leads taken together) do not appear to correlate with the electric position of the hearts.

A study of the direction of the initial component

of the QRS complex in the high sternal area and the adjacent right shoulder reveals that the large Q waves seen occasionally in the V_1 and midline leads of the first 2 intercostal spaces represent an anterior medial extension of the normal Q area of the right upper back and right shoulder.^{2, 14, 15} This fact would suggest a clockwise rotation of the heart—*anatomic or electric*—around its longitudinal axis. While such rotation was present in a few cases showing Q areas in the above-named leads, it was not evident in the majority. A point of some interest is that the zone of transition between the area of initial negativity and that of initial positivity in the anterior right upper chest is often wide open. The initial negative component becomes isoelectric in this transition zone. A QRS complex with an isoelectric initial component would appear, at a cursory glance, to be short in duration, for a portion of it is consumed by the isoelectric initial portion. Such "isoelectric r waves" can be recognized by recording a simultaneous lead with the various chest leads and use it as the time constant against which to time the initial portion of the QRS in chest leads.¹⁵

The incidence of r' in the high anterior leads and particularly those from V_1 , midline and V_2 in the first and second spaces was unexpectedly great (tables 2, 3, and 4). This electrocardiographic item, too, seemed to be unrelated to the position of the mean electric axis of the heart.

ST Segments. The ST segments in the high anterior leads often showed a suggestion of elevation and on occasion as much as 1.5-mm. elevation. Similar but less pronounced elevation of the ST segments can be seen in the conventional precordial leads V_1 to V_4 in a small proportion of normal individuals. No instance of depressed ST segment was seen in any of the high sternal leads.

T Waves. The T waves were invariably negative in V_1 position of first intercostal space and invariably positive in V_4 positions of all 3 intercostal spaces. The intervening leads showed transitions between the 2 extremes (table 5).

It will be evident from this brief discussion and study of tables 2 to 5 that the depolarization complexes display initial positivity in an overwhelming majority of the normal subjects. This r wave is small in leads from the right side of the high sternal area (generally 1 to 3 mm. in amplitude and .01 to .02 second in duration) but it gains both in ampli-

TABLE 2.—*The r Wave in Vertical Hearts*

Vertical hearts 44 cases	1st I.C.S.					2nd I.C.S.					3rd I.C.S.				
	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄
r present	42	41	42	43	44	43	44	44	44	44	44	44	44	44	44
r' present	21	19	18	9	6	10	12	10	6	3	4	4	3	1	1

Duration of r wave in 0.01 sec.

Mean	1.6	1.6	1.8	2.2	2.4	1.7	2.0	2.3	2.6	3.1	2.0	2.2	2.7	3.2	3.8
S.D.±	0.6	0.5	0.7	0.6	0.9	0.6	0.7	0.6	0.7	0.8	0.8	0.7	0.8	0.8	0.8
Mode	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	3.0	3.0	2.0	2.0	3.0	3.0	3.0
Range	0.0	0.0	0.0	0.0	1.0	0.0	1.0	1.0	1.0	2.0	0.0	1.0	1.0	1.0	2.0
	3.0	3.0	3.0	4.0	4.0	3.0	4.0	4.0	4.0	5.0	3.0	3.0	4.0	5.0	5.0

Amplitude of r waves in 1 mm.

Mean	1.5	1.8	1.9	2.2	1.9	2.1	2.7	3.2	3.2	3.3	2.4	3.5	4.6	5.0	6.0
S.D.±	0.80	0.97	0.78	0.88	0.68	1.1	1.5	1.0	1.3	1.2	1.2	1.9	2.2	1.8	2.8
Mode	1.5	2	2	2	2	1	3	3	3	3	3	3	6	5	5
Range	0.0	0.0	0.0	0.0	0.5	0.0	0.5	0.5	1.0	1.0	1.0	1.0	1.0	1.0	2.0
	4.0	4.0	4.0	4.5	4.0	5.0	7.0	7.0	6.0	6.0	8.0	10.0	11.0	9.0	13.0

TABLE 3.—*The r Wave in Intermediate Hearts*

Intermediate hearts (44 cases)	1st I.C.S.					2nd I.C.S.					3rd I.C.S.				
	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄
r present	39	40	43	44	44	44	44	43	44	44	44	44	44	44	44
r' present	16	20	21	16	10	12	15	14	8	3	7	6	4	0	0

Duration of r wave in 0.01 sec.

Mean	1.4	1.5	1.8	2.1	2.8	1.8	2.2	2.4	2.9	3.6	2.1	2.5	2.9	3.7	3.9
S.D.±	0.7	0.8	0.8	0.8	1.2	0.6	0.6	0.7	1.2	0.9	1.0	0.7	1.1	0.9	0.8
Mode	1.0	1.0	2.0	2.0	3.0	2.0	2.0	3.0	2.0	3.0	2.0	3.0	3.0	4.0	4.0
Range	1.0	0.0	0.0	1.0	1.0	1.0	1.0	0.0	1.0	2.0	1.0	1.0	1.0	2.0	2.0
	3.0	0.3	0.3	5.0	6.0	3.0	4.0	4.0	6.0	6.0	4.0	4.0	6.0	6.0	5.0

Amplitude of r wave in 1 mm.

Mean	1.3	1.5	1.8	2.1	3.4	1.4	2.3	2.9	3.7	4.8	2.0	3.1	4.9	7.3	9.4
S.D.±	0.65	0.61	1.3	1.3	2.0	4.2	1.6	2.1	2.2	2.6	0.8	1.9	2.1	1.1	4.0
Mode	1.0	1.5	1.0	2.0	2.0	2.0	2.0	4.0	4.0	4.0	2.0	2.0	6.0	9.0	10.0
Range	0.0	0.0	0.0	0.5	0.5	0.5	0.5	0.5	1.0	2.0	1.0	1.0	2.0	2.0	3.0
	2.0	4.0	9.0	9.0	11.0	3.0	11.0	14.0	13.0	14.0	4.0	9.0	15.0	15.0	20.0

tude and duration as one proceeds toward the left side of the high sternal area (up to 16 mm. amplitude and up to .06 second duration).

The presence of a normal r in high sternal leads is consistent with vectorcardiographic findings in normal subjects. Fowler and Helm¹⁶ studied the initial portion of the vector loop in 18 normal subjects and found it to be directed rightward and anteriorly in 15, leftward and anteriorly in 12, and straight anteriorly in 1. Indeed, all such orientation of the initial vector would give rise to an initial r in high sternal leads. The observations of Grant and Mur-

ray,² Peñaloza and Tranchesi¹⁴ and Wolff, Richmann, and Soffe¹⁷ also indicate that the initial portion of the loop in the majority of normal individuals is expected to point superiorly, anteriorly, and to the right, hence an initial positivity in the QRS complexes recorded from the high sternal area.

Although the general direction of the initial vector in our normal subjects seemed to be superior and anterior, interindividual variations as to the direction in the frontal plane appeared very great. The line of demarcation between the initial Q and initial r varied tremendously from one group to another.

TABLE 4.—The *r* Wave in Horizontal Hearts

Horizontal hearts (18 cases)	1st I.C.S.					2nd I.C.S.					3rd I.C.S.				
	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄
represent....	16	15	18	18	18	16	17	18	18	18	18	18	18	18	18
represent....	10	10	8	7	4	7	7	5	4	2	3	0	1	0	0
Duration of <i>r</i> wave 0.01 sec.															
Mean	1.5	1.6	1.9	2.7	3.3	1.7	2.1	2.6	3.2	3.7	2.3	2.7	3.1	3.6	3.9
S.D.±	0.4	1.1	0.6	1.2	1.1	1.0	0.7	0.6	1.0	0.9	0.9	0.6	0.9	0.7	0.9
Mode	2	2	2	3	4	2	2	3	3	3	3	3	3	4	4
Range	0.0	0.0	1.0	1.0	1.0	0.0	0.0	1.0	2.0	3.0	1.0	1.0	2.0	2.0	3.0
	2.0	3.0	4.0	6.0	5.0	3.0	3.0	4.0	6.0	6.0	4.0	4.0	4.0	6.0	6.0
Amplitude of <i>r</i> wave in 1 mm.															
Mean	1.0	1.3	2.1	3.0	3.5	1.3	2.2	3.6	4.7	7.3	1.8	3.0	5.4	6.9	10.3
S.D.±	.64	.80	1.1	1.9	1.8	1.0	1.1	2.0	2.4	2.9	0.83	1.7	2.0	2.8	3.0
Mode	1.0	1.0	2.0	2.5	2.5	1.0	2.0	4.0	6.0	8.0	2.5	2.5	6.0	6.0	10.0
Range	0.0	6.0	0.5	1.0	1.5	0.5	0.0	1.0	1.0	3.5	0.5	1.0	2.0	2.0	5.0
	2.0	3.0	5.5	8.0	6.0	2.5	4.0	8.0	9.0	14.0	4.0	7.0	12.0	12.0	16.0

TABLE 5.—Direction of *T* Waves, per cent of the Group

	1st I.C.S.					2nd I.C.S.					3rd I.C.S.				
	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄	V ₁	Mid	V ₂	V ₃	V ₄
Vertical															
Positive....	0.0	2.3	9.0	31.8	65.8	4.5	25.0	70.4	84.2	97.7	22.7	70.4	93.3	100	100
Biphasic....	2.3	4.6	15.8	31.8	20.4	9.0	18.1	9.0	6.8	2.3	13.6	6.8	2.3	0.0	0.0
Negative....	97.6	93.1	75.2	36.4	13.6	86.5	56.9	20.4	9.0	0.0	63.7	22.7	4.4	0.0	0.0
Intermediate															
Positive....	0.0	11.3	29.5	56.9	88.5	9.0	38.7	81.9	95.4	97.7	31.8	77.3	95.4	97.7	100
Biphasic....	6.8	6.8	11.3	18.1	4.5	2.3	13.6	11.3	2.3	2.3	15.9	2.3	2.3	0.0	0.0
Negative....	93.2	81.9	59.2	25.0	6.8	88.5	47.7	6.8	2.3	0.0	52.2	20.4	2.3	2.3	0.0
Horizontal															
Positive....	5.5	16.6	44.4	94.5	100	16.6	66.6	100	100	100	38.8	88.8	100	100	100
Biphasic....	0.0	11.1	22.2	0.0	0.0	11.1	22.2	0.0	0.0	0.0	16.6	0.0	0.0	0.0	0.0
Negative....	94.5	72.3	33.3	5.5	0.0	72.3	11.1	0.0	0.0	0.0	44.4	11.1	0.0	0.0	0.0

and even in the individuals of the same group. The overlap was so great as to make estimation of the position of this line on the basis of the main vector impossible. This may be due to individual variations in the activation of the septum and/or other structures responsible for the genesis of the initial depolarization forces such as the crista supraventricularis. Such variations have been found in intracavity leads of normal individuals as shown by Levine and co-workers¹⁸ and Kossman and his associates.¹⁹

Conclusion. This study of the normal electrocardiogram of the high anterior area indicates that the presence of an *r* in these leads taken as a group is very common; a *Q* wave in the V₁ and midline leads occurs with sufficient frequency to make it useless as a diagnostic item for classical usage; a *Q* wave in V₂, V₃, and V₄ leads is seen very uncommonly, hence

of diagnostic significance. The 2 positions pointed out previously, namely V₂, 2 i.c.s. and midline, 3, i.c.s., show initial positivity in almost 100 per cent of the normal individuals.

Owing to the marked overlapping of the *r* and *Q* area of the anterior leads in normal subjects, the finding of a *Q* wave in the 2 leads mentioned cannot be safely considered pathognomonic of infarction. Like any other electrocardiographic item, this must be interpreted in the light of the clinical condition of the patient. Right ventricular dilatation and hypertrophy, right bundle-branch block, left ventricular hypertrophy, and left bundle-branch block must be ruled out before determining the value of a *Q* in high anterior leads for such conditions can displace the normal *Q* area to the left and inferiorly.²⁰⁻²³ Likewise it is necessary to differentiate

between a true Q and a "pseudo-Q" caused by iso-electricity of the r wave.

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Indications and Contraindications for the Use of Molar Sodium Lactate

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The experience with molar sodium lactate has been extended to include 101 patients. Certain indications and relative contraindications to its use have crystallized. Administration of this agent is shown to be a physiologic and effective method for treating patients with severe hyperpotassemia, multiple Stokes-Adams attacks, and cardiac arrest, particularly that occurring in the operating room complicating cardiac surgery. For many patients in these categories, sodium lactate was life saving even though it was generally given after other more commonly used drugs and methods of therapy had proved ineffective in restoring cardiac rhythm. In the total group of patients untoward effects were few.

THE initial work on the use of molar sodium lactate was reported from this laboratory in May, 1955,¹ on the basis of a series of 6 cases. At that time its use was discussed in the following conditions: restoring cardiac beating during cardiac arrest in Stokes-Adams attacks and during episodes of cardiac arrest of other etiologies, and increasing the slow ventricular rates of sinus bradycardia and partial and complete A-V heart block. The rationale was based on an entirely different principle in therapy from that previously used in the human subject (e.g., atropine and sympathomimetic drugs). Its efficacy apparently depends upon an alteration in the electrolyte pattern in the extracellular fluid, which becomes more physiologic or tends to increase cardiac rhythmicity. Since this report, further communications²⁻⁴ amplified these initial observations, which included our preliminary impressions regarding the dose, route, and speed of administration, toxic effects, and possible modes of action. Subsequently, our experience has been extended to include a total of 101 patients. In these we have been able to study more completely the place of molar sodium lactate in the

situations mentioned above and in addition have elaborated on 2 other conditions in which it has manifested salutary effects.

RESULTS

Table 1 summarizes the number of subjects in each of the different categories studied. For the sake of conciseness only the pertinent data in each category will be briefly discussed.

A. The data on the effects of molar sodium lactate in normal patients have been previously presented. No untoward effects were observed.²

B. Ten patients, ranging in age from 52 to 81 years, manifested clinical and electrocardiographic evidence of varying degrees of myocardial abnormality and myocardial damage (including partial A-V block). Untoward effects were observed in 4 patients and consisted of transient T-wave inversion (2 cases) and transient extrasystoles (2 cases).^{2, 3} These effects were observed in older patients who presented a severe grade of myocardial damage; they were transient and persisted for only 1 or 2 minutes after cessation of the infusion. In the presence of partial A-V block (6 cases) the alterations in the atrial and ventricular rates were slight and insignificant in the doses given. The chief exception was observed in the presence of atrial fibrillation with slow ventricular rates ranging from 40 to 60 per minute (3 cases). In these patients the ventricular rate was significantly increased (by 10 to 40 beats per minute) following the infusion.

C. In 6 of 8 patients who had evidence of myocardial abnormality with sinus bradycardia there was a significant increase in the ventricu-

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TABLE 1.—*Classification of Cases*

Code	Type of cases	Number of cases previously reported	Total cases to date
A	Normal subjects	5	5
B	Myocardial damage (including partial A-V block)	10	10
C	Sinus bradycardia	6	8
D	Asymptomatic complete A-V block	12	17
E	Stokes-Adams (ventricular standstill, ventricular flutter, and ventricular fibrillation)	4	17
F	Cardiac arrest during surgery	0	12
G	Terminal cardiac arrest	12	20
H	Hyperpotassemia of various etiologies	2	12
Total		51	101

lar rate. Two instances of nodal escape were abolished as the ventricular rates increased. There was only a slight increase in the ventricular rate in the remaining 2 cases. No untoward effects were observed in this group.

D. These patients with asymptomatic complete A-V block ranged in age from 55 to 80 years, with an average of 66 years. Most of the patients manifested an advanced grade of arteriosclerosis. The atrial rhythm was of sinus origin in 14 and atrial fibrillation was present in 3 cases. In the 3 subjects with atrial fibrillation the ventricular rates increased from 32 to 38, 39 to 48, and 45 to 52 per minute, respec-

tively. In the former group with sinus rhythm, molar sodium lactate administered in doses of 100 to 150 ml. in 10 to 15 minutes was effective in increasing the ventricular rate in 6 cases; in 5 of these 6 the increase ranged from 4 to 12 beats a minute, with an average of 8 beats per minute (an increase of from 10 to 20 per cent over the control level); in the sixth case an initially rapid ventricular rate increased from 71 to 100 beats per minute. In the remaining 8 cases no effect was observed on the ventricular rate. In 3 of these cases isolated ventricular extrasystoles appeared, which were not present in the control tracing; these disappeared within a few minutes after the drug was stopped. Two patients who showed frequent ventricular extrasystoles in the control tracing developed runs of ventricular extrasystoles leading to ventricular tachycardia during the course of the infusion (fig. 1). These disappeared within 2 to 3 minutes after cessation of the infusion. It is of interest that 1 of the 2 patients who developed ventricular tachycardia had a serum potassium of 2.7 mEq. per L. prior to the administration of sodium lactate. In this same patient the intravenous and intramuscular administration of procaine amide produced ventricular flutter and ventricular fibrillation. In general the cases in this group who developed extrasystoles manifested rather severe grades of myocardial disease and belonged in the older age group.

E. The 17 patients with Stokes-Adams seizures were divided into 2 groups: (1) 10 patients had multiple Stokes-Adams attacks

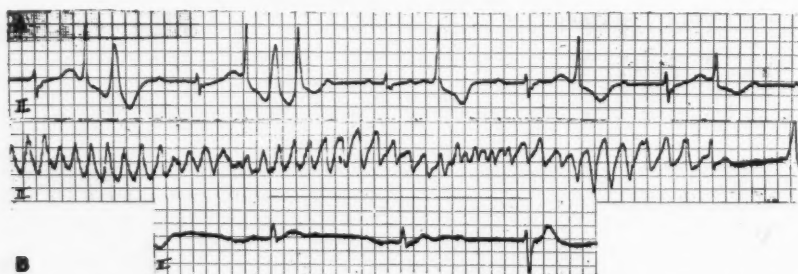


FIG. 1. Effect of molar sodium lactate in a patient with complete A-V block and ventricular extrasystoles in the control tracing. *A.* Control tracing showing complete A-V block and frequent extrasystoles, some of which occur in groups of two and three. *B.* Continuous record, 4 minutes after 100 ml. of molar sodium lactate in 10 minutes, showing transient ventricular flutter and fibrillation. The patient died 12 hours later.

TABLE 2.—Ten Patients* with Frequent Stokes-Adams Attacks

Case no., age, and sex	No. of attacks	Other drugs used before molar sodium lactate	Results with other drugs	Molar Sodium Lactate		Ultimate fate	Results and remarks
				Amount	Duration of infusion		
1 7 C	About 100 in 18 hrs.	Neosynephrine, atropine	Progressive increase in frequency of seizures	360 ml. ($\frac{1}{4}$ molar) 1000 ml. (0.5 molar)	30 min. 3 hrs.	Died 18 hrs. after admission to hospital	Each episode characterized by ventricular standstill. Immediately following the SL the episodes ceased and the beating continued as long as the infusion was running. SL was successful on repeated trials.
2 7 C	4-10 daily for 10 days	Epinephrine in oil, ephedrine	Ineffective in controlling frequency of seizures	40-80 ml. i.v.	1-2 min.	Survived	Attacks of 2 types: standstill and ventricular tachycardia-flutter. MSL effective in both types.
3 6 C	8-10 a day for 5 days	Epinephrine (in oil and aqueous), ephedrine, Isuprel	Ineffective in controlling seizures but frequency decreased	100 ml. i.v.	60 min.	Survived, left hospital with NSR	After MSL the normal sinus rhythm with RBBB appeared. After 6 weeks at home on oral MSL 100 ml. 4 i.d., NSR still present.
4 65 C	4 in 24 hrs.	Ephedrine, Isuprel, epinephrine, atropine	Ineffective	500 ml. ($\frac{1}{6}$ molar) i.v.	30 min.	Survived	Seizures ceased after MSL
5 83 C	15 in 6 hrs.	Isuprel, ephedrine, atropine	Ineffective	240 ml. i.v.	4 hrs.	Died 10 days later	Immediate restoration of cardiac beating and cessation of attacks. On a second trial 10 days later while on Isuprel, ephedrine, and atropine, MSL was ineffective and the patient died.
6 94 C	40 in 1 hr.	Isuprel	Ineffective	1000 ml. i.v.	6 hrs.	Died 9 hours after admission to hospital	Mechanism of S-A seizures was ventricular tachycardia-flutter-fibrillation; MSL markedly decreased the frequency of these episodes but did not stop them. Responded best to combination of epinephrine and MSL by slow iv drip.
7 79 C	multiple	Epinephrine, atropine in oil, Metrazol	Ineffective	240 ml. i.v.	30 min.	Survived	This patient continued to have frequent S-A attacks while on an electric pacemaker. Spontaneous ventricular beating returned 30 min. following i.v. MSL and the patient was taken off the external electric pacemaker after 40 hrs. of continuous use.
8 65 C	6-12 per hr.	Epinephrine	Ineffective	120 ml. i.v.	30 min.	Survived	MSL restored cardiac beating and terminated S-A attacks on repeated trials on different days. Return first degree A-V block.
9 71 C	20 episodes in 4 hrs.	Norepinephrine to maintain blood pressure	Ineffective	120 ml. rapidly 4 hrs. later 80 ml. rapidly		Survived	MSL stopped the episodes of ventricular standstill. There was a transient return to NSR for about 1 min. following which complete A-V block returned. No change in conduction on a second trial.
10 77 C	6 in 2 hrs.	Epinephrine, norepinephrine	Effective in controlling the seizures	180 ml. i.v.	2 hrs.	Died 5 days after admission of unrelated disease	Decreased frequency and finally abolished episodes of ventricular standstill (longest one lasted 57 seconds).

* All these patients had arteriosclerotic cardiovascular disease; complete A-V block was the basic rhythm in every case, atrial fibrillation was present in case 10. An old myocardial infarction was present in case 2 and a subacute infarction in case 10.

S-A = Stokes-Adams.

MSL = Molar sodium lactate; used unless otherwise indicated.

iv = Intravenous.

NSR = Normal sinus rhythm.

occurring within a short period of time (table 2); (2) 7 patients showed either isolated episodes of cardiac arrest occurring at longer intervals of time or a single attack of variable duration.

It is often difficult to evaluate the efficacy of a particular form of therapy for isolated Stokes-Adams seizures, since the episodes often spon-

taneously stop. The exact relationship, therefore, between the effect observed following molar sodium lactate in the second group of 7 patients, whether it was coincidental or a result of the drug, was more difficult to establish, since the Stokes-Adams attacks showed no definite pattern for comparison. For this reason we are not including the effect of sodium

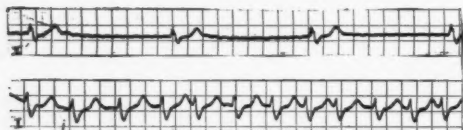


FIG. 2. Effect of molar sodium lactate on a 71-year-old man with atrial fibrillation and complete A-V heart block with a slow ventricular rate. *Top.* Control. Lead I shows atrial fibrillation with complete A-V heart block. The ventricular rate is approximately 32 per minute and the QRS complexes measure 0.14 second in width. *Bottom.* Lead I, 9 seconds after starting molar sodium lactate intravenously. Approximately 5 ml. have been given. The ventricular rate has increased to approximately 115 per min. The QRS width remains about 0.14 second. This effect was repeatedly reproduced in this patient.

lactate therapy in restoring cardiac beating in this group of patients.

In patients with repeated Stokes-Adams episodes occurring within the space of a few hours, particularly when they present a relatively uniform pattern, character and duration, the effect of intravenous drug therapy can be judged with much greater reliability. Molar sodium lactate was successful in the first group of 10 patients in restoring ventricular beating in 7 cases during many repeated trials (in the majority of cases 10 or more trials). With repeated episodes of ventricular standstill the rapid infusion of molar sodium lactate consistently restored ventricular beating. In 4 of these cases where electrocardiographic records are available the rate of the idioventricular pacemaker could be directly related to the rate of the intravenous infusion. As the rate of the infusion was speeded the idioventricular rate increased above the control rate; it subsequently slowed, on repeated trials, as the rate of the infusion was purposely slowed (fig. 2 and fig. 1 of reference 1). Table 2 summarizes the pertinent data on the 10 patients with multiple Stokes-Adams seizures occurring within a brief period of time. The average age of these patients was 75 years. Most patients (7) had received 2 or more frequently used agents for the treatment of Stokes-Adams attacks prior to the molar sodium lactate. The most commonly used drugs were sympathomimetic [epinephrine, phenylephrine (Neosynephrine), isopropylnorepinephrine (Isuprel), and ephed-

rine] and parasympatholytic agents (atropine). In case 10 sympathomimetic agents temporarily stopped the Stokes-Adams seizures, and in case 6 the combination of sympathomimetic agents and molar sodium lactate appeared to be more effective than either drug alone. Restoration of ventricular beating after sodium lactate occurred in 2 patients (cases 2 and 6) in spite of episodes of ventricular flutter and fibrillation. Case 6 is particularly interesting in that the mechanism of all of the many Stokes-Adams seizures was paroxysmal ventricular tachycardia-flutter and fibrillation. The intravenous administration of molar sodium lactate markedly diminished the frequency of these paroxysms (fig. 3). In 2 instances (cases 5 and 6), however, the molar sodium lactate solution, although initially effective, ultimately failed to influence the episodes of cardiac standstill and death ensued.

Six of these 10 patients survived (cases 2-4, 7-9) and were ultimately discharged from the hospital. In 5 of the 6 the administration of molar sodium lactate was apparently life-saving. Other similar patients have been reported who responded to sodium lactate after sympathomimetic and vagolytic drugs had failed.^{5, 6} Patient 7 continued to have episodes of ventricular standstill while on the artificial electric pacemaker and showed no signs over a 40-hour period of observation of spontaneous idioventricular beating. Thirty minutes after intravenous molar sodium lactate the pacemaker was discontinued and the spontaneous idioventricular beating continued; this patient was ultimately discharged from the hospital 6 weeks later. Curiously enough, none of these patients with multiple Stokes-Adams attacks in association with complete A-V block manifested extrasystoles, during the period of observation, even after large amounts of the drug.

F. Molar sodium lactate was used in 12 cases of cardiac arrest occurring during surgery. Surgery was performed for the following conditions: congenital heart disease (5 patients), calcific aortic stenosis (3 patients), mitral insufficiency (2 patients), mitral stenosis (1 patient), mitral insufficiency and mitral stenosis (1 patient). In some of these cases molar sodium lactate was effective in restoring the heart beat

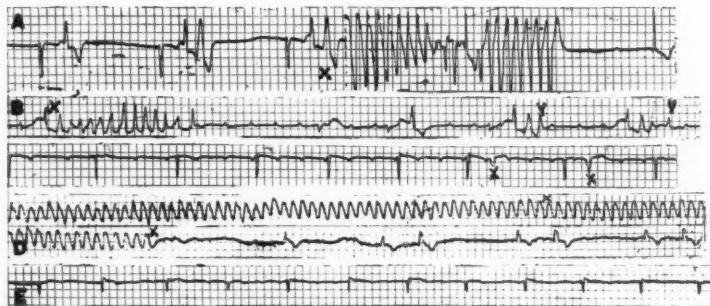


FIG. 3. Case 6 in table 2, aged 94, with arteriosclerotic heart disease. Effect of molar sodium lactate on repeated Stokes-Adams seizures due to ventricular tachycardia-flutter and fibrillation. *A.* Lead V_3 at 7:15 p.m., showing complete heart block and ventricular tachycardia-flutter, originating from different foci. The frequency of the paroxysms of ventricular tachycardia-flutter and syncope decreased markedly after 20 ml. of molar sodium lactate. *B.* Lead V_1 at 8:40 p.m. after 1 hour and 15 minutes without lactate, showing a run of ventricular tachycardia-flutter at *X*. At *Y*, are ventricular extrasystoles, which increased in frequency. *C.* Lead V_1 at 9:00 p.m. after approximately 50 ml. of molar sodium lactate was given in 5 minutes. Only 2 extrasystoles occur, marked *X*, a striking decrease compared with *B*. *D.* Lead II, a continuous tracing at 10:05 p.m. The patient received 20 ml. of sodium lactate from 8:55 to 9:15 p.m. The patient has received 50 ml. of isotonic sodium chloride from 9:20 to 10:05 p.m. At the first *X* during ventricular flutter 40 ml. of molar sodium lactate were given intravenously rapidly in 1 minute; 9 seconds later, at the next *X*, the ventricular flutter stopped and idioventricular rhythm returned. *E.* Lead V_1 at 10:15 p.m. There are no extrasystoles. The ventricular rate has slowed to approximately 35 per minute.

after other measures, including cardiac massage, electric defibrillation, and sympathomimetic drugs (epinephrine, Neosynephrine, and Isuprel), employed over a period of 10 to 15 minutes were ineffective.^{3,7} In this group of 12 patients, molar sodium lactate restored effective cardiac beating in 7 cases. One of them died 7 hours after resuscitation; another died 15 hours postoperatively, and a third died within 24 hours; 4 survived and were ultimately discharged from the hospital. Table 3 summarizes the pertinent data on the 7 patients in whom molar sodium lactate was apparently successful in resuscitating the heart.

Although the total number of cases presented above indicates a high percentage of survival, it does not represent an accurate percentage of the survival rate during surgery; there were other instances where molar sodium lactate was used unsuccessfully in conjunction with other resuscitative measures in the treatment of cardiac arrest during surgery.

G. The 20 cases of terminal cardiac arrest included patients dying from carcinomatosis, cerebrovascular accidents, acute myocardial infarction, and a number of other morbid states.

In many of these patients no lasting resuscitation could have been achieved and, therefore oxygen and artificial respiration were not used. In others the time interval from cessation of cardiac beating to resuscitative attempts was so long that the chance of reviving the patient was gone. In the cases seen within 2 to 3 minutes following ventricular standstill, successful restoration of cardiac beating of variable duration was frequently encountered. Two such cases have been previously reported;^{1,4} in them the administration of sodium lactate, oxygen, and artificial respiration resulted in a gradual elevation of the blood pressure to normal levels, improvement in the skin color and a return of the electrocardiogram to a normal configuration. Our experience with terminal cardiac arrest suggests that where the cause of the arrest is a sudden process (independent of a chronic incurable disease), the administration of molar sodium lactate together with other resuscitative measures might resuscitate the heart, much as it has in the surgical group.

In the presence of cardiac arrest occurring during Stokes-Adams seizures and occurring terminally, the question often arises how the

TABLE 3.—Seven Patients with Cardiac Arrest during Surgery and Cardiac Resuscitation with Molar Sodium Lactate

Case no., age, and sex	Diagnosis	Surgical approach	Other resuscitative measures	Molar sodium lactate		Ultimate fate	Remarks
				Amount given	Duration of infusion		
1 42 ♀	Interatrial septal defect	Direct vi- sion with hypother- mia	Atropine, adren- alin, electric defibrillation, manual com- pression	450 ml.	4 hrs.	Discharged from the hospital	Sodium lac- tate started 15 min. after onset of cardiac arrest
2 53 ♂	Severe cal- cific aor- tic steno- sis	Transaortic	Manual com- pression, elec- tric defibril- lation, atro- pine	300 ml. iv 2700 ml. iv	20 min. 18 hrs.	Discharged from the hospital	Sodium lactate started after 25 min.
3 29 ♀	Giant left atrium and severe mitral insuffi- ciency	Left atrial	Electric defibril- lation, nor- epinephrine, epinephrine, Isuprel	500 ml. iv	1½ hrs.	Died 7 hrs. postop- eratively	At necropsy suture found 1 cm. from the A-V node
4 11 mos. ♂	Pulmonic stenosis with pa- tent for- amen ovale	Transven- tricular	Manual compres- sion, atropine	30 ml. iv	20 min.	Discharged from the hospital	MSL restored effective cardiac contrac- tions
5 6 mos. ♀	Ventricular septal de- fect	Open technic with pump - oxygena- tor	Manual compres- sion, atropine	10 ml. iv	10 min.	Died 15 hrs. postop- eratively	
6 9 mos. ♀	Pulmonic atresia and te- tralogy of Fallot	Transven- tricular	Manual compres- sion, atropine	10 ml. iv	5 min.	Died 24 hrs. postoper- atively	Tetralogy of Fallot at necropsy
7 42 ♀	Mitral stenosis	Left atrial	Manual compres- sion, iv norepi- nephrine and intracardiac Methoxamine, calcium-chlo- ride and pro- caine 2 per cent, electric defibrillation	250 ml. iv (.5 MSL) 40 ml.	10 min. 5 min.	Discharged from the hospital	MSL appar- ently life- saving, was started 22 min. after onset of cardiac ar- rest

sodium lactate reaches the heart. If the drug is given intravenously rapidly, within one-half to 1 minute after the arrest, a cardiac effect may be produced, particularly if artificial respiration has been instituted. The respiratory movements create negative pressure in the chest and thereby promote the return of blood to the heart. With longer periods of arrest the effect

of the intravenous injection is less evident, even when given rapidly and in extremely large doses in conjunction with artificial respiration. In such instances one must resort to slow intracardiac injection.

H. Hyperpotassemia kills by its cardiotoxic effects. The usual electrocardiographic manifestations of severe potassium poisoning are a

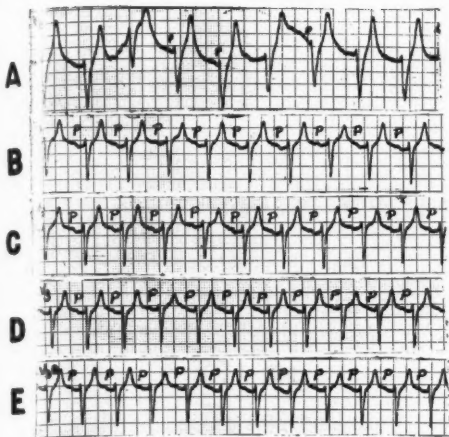


FIG. 4. Effect of molar sodium lactate in hyperpotassemia in a 75-year-old patient with hypertension, nephrosclerosis, and uremia. A. Lead V_3 at 9:00 p.m. There is a regular ventricular rate at 83 per minute, with QRS complexes widened to 0.14 second, and independent of the P waves. The serum K was 7.8 mEq./L. and no blood pressure was obtained. B. Lead V_3 at 9:15 p.m. after 80 mEq. molar sodium lactate in 10 minutes. The blood pressure was 130/90. The ventricular rate is faster. The QRS complexes are narrowed to 0.10 second and the T waves are less tall. There is regular A-V conduction with a P-R of 0.22. C. Lead V_3 at 9:17 p.m. after 90 mEq. sodium lactate in 12 minutes. The QRS complexes are 0.08 wide and the P-R interval is 0.20 second. D. Lead V_3 at 9:19 p.m. after approximately 97 mEq. sodium lactate in 14 minutes. The ventricular rate is approximately 104 per min.; the P-R interval is 0.18 second. E. Lead V_{3R} at 9:20 p.m. after 100 mEq. sodium lactate in 15 minutes. The blood pressure remained at 130/90; there was marked clinical improvement, and the sodium lactate was stopped.

slow idioventricular rhythm with widened QRS complexes and absent P waves; less frequently tachycardia is present. The hyperpotassemia in the 12 cases³ was of an advanced

grade often associated with or secondary to uremia, with a concomitant shock-like state and characteristic electrocardiographic changes of advanced potassium intoxication. The serum potassiums ranged from 6.4 to 10.7 mEq. per L. Molar sodium lactate had a prompt and salutary effect not only on the electrocardiographic but also on the circulatory changes. The clinical picture in almost all cases was vastly improved. The ultimate outcome of the patients was primarily determined by the extent and reversibility of the renal damage. Two of the 12 patients were discharged from the hospital; 2 were terminal on admission; and the remaining 8 patients lived from 15 hours to 30 days after treatment. In these 12 cases we have not encountered a single instance in which molar sodium lactate failed to improve or to reverse entirely the electrocardiographic changes due to potassium poisoning (figs. 4 and 6). Generally the clinical and electrocardiographic evidence of improvement appeared within 2 to 30 minutes following the infusion of molar sodium lactate. No extrasystoles were observed in the 12 cases; 2 anuric patients, however, developed pulmonary congestion after treatment with sodium lactate.

While most efficacious in acute potassium intoxication, the solution was also used for insidiously developing hyperpotassemia and acidosis. This group of patients is of particular importance since in them we have been able to prevent cardiac arrest as a cause of death with sodium lactate.

The electrocardiogram of the dying heart resembles that of hyperpotassemia. Reversal of the manifestations of depressed ventricular rhythmicity might explain some of the recoveries observed in the terminal cases as well

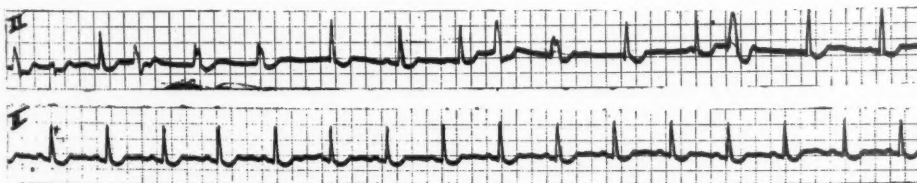


FIG. 5. (Lead II) Effect of sodium lactate on multiple premature ventricular contractions in a patient with arteriosclerotic heart disease. Top. Control. Normal sinus rhythm interrupted by numerous ventricular, nodal, and aberrant supraventricular beats. Bottom. Two minutes after sodium lactate, regular sinus rhythm without extrasystoles.

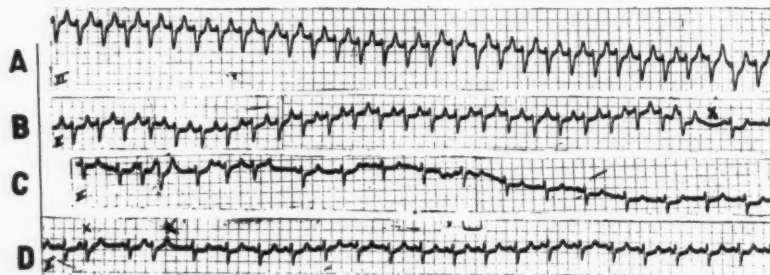


Fig. 6. A 51-year-old woman with hypertensive cardiovascular disease and uremia. Conversion of a paroxysmal supraventricular tachycardia due to hyperpotassemia to normal sinus rhythm by molar sodium lactate was recorded in 3 repeated trials. Approximately 100 mEq. of molar sodium lactate administered in 2 minutes prior to A was continued from A to D at the rate of 200 drops per minute. A. Lead 2. Supraventricular tachycardia with a ventricular rate of 130 per min. Atrial activity is discernible only toward the end of the strip. The T waves are tall and peaked. The QRS complexes measure 0.11 second. The serum potassium was 7.6 mEq./L. B. P waves are more definite. At X is a pause followed by conducted sinus beats. The QRS complexes have narrowed to 0.08 second. C. Normal sinus rhythm with several aberrant beats is present. The T waves are less tall, but still peaked and the Q-T segment is prolonged, suggesting coexistent hypocalcemia. D. More normal tracing with occasional supraventricular beats at X and coincidental clinical improvement.

as those in which anoxia resulted in a sudden increase in the extracellular potassium, which would also depress the cardiac pacemakers.

DISCUSSION

Indications and Dosage of Molar Sodium Lactate

The experience to date suggests that molar sodium lactate is indicated in the following conditions:

A. Hyperpotassemia

Dosage. 1. In patients with electrocardiographic evidence of advanced potassium intoxication 100 ml. of molar sodium lactate was usually administered intravenously rapidly (in 1 to 2 minutes) followed by an intravenous infusion at a rate of approximately 30 to 60 drops per minute; the total amount given is dependent upon the effects observed; for example, in a reversion from a stage 3 or stage 4 (slow idioventricular rhythm with markedly aberrant ventricular complexes) to a stage 1 (tall, peaked T waves). 2. In patients with early electrocardiographic evidence of hyperkalemia, an intravenous infusion may be given at the rate of 15 to 30 drops per minute until the desired effects are observed.

B. Stokes-Adams Attacks

Since molar sodium lactate has a relatively short effect of about 2 hours it is not indicated

unless the patient is having frequent, repeated episodes or, perhaps, at the precise time of a solitary attack. For the occasional or isolated Stokes-Adams episode long-acting sympathomimetic drugs are the preferred method of treatment. We have recently been using oral molar sodium lactate 90 ml. q.i.d. with promising results in an attempt to prevent or abort these occasional attacks.

Dosage. For multiple Stokes-Adams attacks, 40 to 80 ml. may be given intravenously in 1 to 2 minutes during an attack and may be followed by an intravenous infusion at the rate of 60 to 150 drops per minute, the exact rate and the total amount given being dependent upon the effects observed. As the ventricular rate increases the infusion should be slowed; when the pacemaker maintains a satisfactory rate and the episodes of cardiac arrest are abolished, the infusion should be stopped. From 240 ml. within 30 minutes to 1000 ml. in 6 hours have been given without untoward effects (table 2).

C. Cardiac Arrest During Surgery

The exact conditions under which sodium lactate is best employed for this condition requires further investigation.

Dosage. 1. When cardiac contractions are slow but effective or manual compression is

effective in maintaining adequate circulation, molar sodium lactate may be given intravenously at a rate of 100 to 200 drops per minute, approximately 7 to 14 ml. per minute. 2. In the presence of ventricular standstill or ineffectual manual compression or when the initial dosage of sodium lactate has not been effective, 20 to 40 ml. may be given slowly into the right ventricle at a rate of approximately 3 to 5 ml. per minute. 3. In infants, an intravenous infusion may be administered at a rate of approximately 1 ml. per minute while manual compression is continued.

D. Sudden Cardiac Arrest

The dose and route of administration of sodium lactate for these situations have not been ascertained. In a general way the schedule outlined for arrest during surgery should be followed.

Mechanism of Effects

The mechanism of action of molar sodium lactate in increasing cardiac rhythmicity is still under investigation. The following mechanisms were originally postulated^{1,4}: (a) the production of alkalosis increased the irritability of the myocardium, (b) the increase in the sodium raised the height of the action potential, (c) the lactate provided additional fuel for the heart, (d) a vagolytic effect increased the cardiac rate.⁹ Recently, we have suggested that one of the major factors is a decrease in the potassium in the extracellular fluid, which is accomplished by expansion of the extracellular space and movement of potassium intracellularly.^{7, 10} A markedly increased rhythmicity of cardiac pacemakers by a low serum potassium has recently been documented in man and animals.^{8, 10-12} A more favorable Na:K ratio is probably an additional factor. The effects on rhythmicity, while due chiefly to a variation in extracellular potassium, may be influenced indirectly by other electrolytes, e.g., sodium, calcium, and to a lesser degree, by magnesium.

Comparison of Sodium Lactate with Sodium Bicarbonate and Sodium Chloride

The original purpose of giving molar sodium lactate was to use a convenient, established,

and relatively safe method of producing a mild grade of alkalosis. As far as we know, this principle was previously employed in the perfused heart,¹³⁻¹⁶ but has never been used in the intact animal or the human subject to increase cardiac rhythmicity. Substances with similar action may produce qualitatively similar effects (e.g., sodium bicarbonate), but sodium bicarbonate may be somewhat more toxic^{17, 18} than sodium lactate, since it produces a marked shift in the pH quite rapidly. After our original observations we have studied the effect of sodium bicarbonate clinically and experimentally, for example, in hyperkalemia in the nephrectomized dog; while the results are qualitatively similar, they are less marked with sodium bicarbonate and of shorter duration than with molar sodium lactate.¹⁰ Sodium chloride was even less effective than sodium bicarbonate.¹⁰ The chloride radical is a powerful anion, which tends to decrease the pH, thereby preventing or minimizing the decrease in extracellular potassium.

In summary, while similar in effect to sodium bicarbonate and sodium chloride, thus far molar sodium lactate would appear to be superior to them in the clinical states mentioned above.

Toxic Effects and Contraindications

Patients with complete A-V block are especially subject to develop ectopic rhythms because of areas of increased or decreased irritability in the heart muscle. The nodal or idioventricular pacemaker is notoriously unstable and any factor that increases cardiac work, such as the rapid infusion of fluid or hypertonic solutions (molar sodium lactate), might precipitate ectopic rhythms of various types. This is particularly likely when there are ectopic beats in the control tracing.

Extrasystoles are an important evidence of toxicity due to molar sodium lactate. They could result from the sudden increase in cardiac work or the lowering of serum potassium as a consequence of the production of or aggravation of alkalosis. Obviously, this toxic effect would tend to occur more commonly in the presence of established cardiac irritability, either latent or manifested by extrasystoles. In a general way, patients with severely diseased hearts

and those with complete atrioventricular block belong in this category.

In early observations we showed that molar sodium lactate would increase cardiac rhythmicity in asymptomatic complete atrioventricular block.^{1, 3, 4} The ventricular rate increased in 9 patients of this type (53 per cent); however, extrasystoles were produced or were increased by molar sodium lactate in 5 subjects (29 per cent). *We do not recommend molar sodium lactate for routine use in these cases of asymptomatic complete heart block, nor are sympathomimetic drugs routinely given to this group.*

With the cessation of the infusion of molar sodium lactate the ectopic rhythm disappeared in a few seconds or minutes. It seems to us that this rapid cessation is less true of ventricular tachycardia resulting from the use of epinephrine or Isuprel; in these instances the effects are not easily reversible and ventricular fibrillation frequently ensues.

It is well documented that epinephrine may produce ventricular fibrillation, particularly in a damaged heart. Isuprel also tends to produce ventricular ectopic beats and ventricular fibrillation. Recently Zoll and co-workers¹⁹ stated, "epinephrine, norepinephrine, and isopropylnorepinephrine differed only quantitatively . . . Isopropylnorepinephrine sometimes excited multifocal ventricular activity in the same dose required to arouse an idioventricular pacemaker; the effect on the blood pressure, if any, was a depressor one."

The abolition or notable decrease of extrasystoles and of paroxysmal tachycardia after molar sodium lactate presents an interesting phenomenon. This was observed in 3 cases with extrasystoles (fig. 5) and in 2 subjects with paroxysmal supraventricular tachycardia associated with hyperpotassemia (fig. 6). While the mechanism in the latter group is more easily understandable, it is more difficult to explain the former. The following possibilities may be considered: (a) mild forms of hyperkalemia may have been unrecognized, (b) an increased ventricular rate resulting from the lactate may prevent discharge of ectopic foci, and (c) the lactate ion might improve cardiac function by acting as a fuel.

The presence of ventricular extrasystoles occurring in association with complete atrioventricular block presents a difficult therapeutic problem. Many of these patients have additional complicating factors: coronary artery disease with chronic or subacute myocardial infarction, congestive heart failure, electrolyte imbalance, or some other cause of cardiac irritability. Unless the extrasystoles are the result of a transient reversible factor, the prognosis in this group is poor, since they have an increased susceptibility to the development of ventricular tachycardia and ventricular fibrillation, leading to potentially fatal Stokes-Adams attacks. The use of quinidine or procaine amide is contraindicated because, while these drugs may abolish the extrasystoles, they further depress already depressed ventricular pacemakers. Sympathomimetic drugs in the form of epinephrine or Isuprel are also dangerous because of their tendency to increase cardiac irritability, which may increase the rhythmicity of the idioventricular pacemaker, but in our experience has also increased the frequency of the ventricular premature contractions and caused runs of ventricular tachycardia.

In summary, the following circumstances either contraindicate the use of molar sodium lactate or indicate extreme caution in its use; (1) the appearance or increased frequency of extrasystoles following the administration of sodium lactate; (2) severe heart damage, particularly in association with overt or impending congestive heart failure; (3) hypokalemia or alkalosis.

SUMMARY

Since our initial observations of the cardiovascular effects of molar and 0.50-molar sodium lactate, we have extended our experience to include 101 patients. Its value in certain clearly defined conditions has become apparent. In these sodium lactate has proved to be an extremely valuable addition to the therapeutic regimen.

Molar sodium lactate is shown to be a physiologic, safe, and rapid means of reversing the cardiotoxic manifestations of severe hyperpotassemia. The drug was successfully used in

10 patients with multiple Stokes-Adams seizures that occurred within a brief period of time, generally after sympathomimetic and vagolytic agents had been either totally ineffective or only partially effective. In addition, 12 cases of cardiac arrest occurring during intracardiac surgery were treated with molar sodium lactate within variable periods following the cardiac arrest—7 were successfully resuscitated for varying periods of time and 4 ultimately lived and were discharged from the hospital. In general, the usual therapeutic measures for cardiac arrest had been unsuccessfully tried prior to the administration of molar sodium lactate.

The presence of extrasystoles in the control tracing either contraindicates the use of sodium lactate or makes it mandatory that it be given with extreme caution under constant electrocardiographic control. An increase in pre-existing extrasystoles, short paroxysms of ventricular tachycardia, and the new development of extrasystoles have been observed. Congestive heart failure may also develop as another untoward effect of sodium lactate therapy.

Although qualitatively similar in its effects, molar sodium lactate was somewhat more effective over a longer period of time than sodium bicarbonate.

Preliminary comparisons with epinephrine and Isuprel have suggested that molar sodium lactate manifests less profibrillatory qualities when used in comparable effective doses under similar conditions. Because its action is based on a different principle from that of the vagolytic and sympathomimetic drugs, it may supplement these agents, and may also be effective in conditions where the others are entirely useless.

SUMMARY IN INTERLINGUA

Depost nostre observationes initial in re le effectos cardiovascular de lactato de natrium in solutiones de 1 o 0,5 M, nos ha extendite nostre experientia a un serie total de 101 patientes. Le valor del medication in certe clarmente definite conditiones es nunc evidente. In iste conditiones, lactato de natrium se ha revelate como un utilisime addition al regime therapeutic.

Molar lactato de natrium es un medio physiologic, salve, e rapide pro reverter le manifestationes cardiotoxic de sever hyperkalemia. Le droga esseva usate con successo in 10 patientes con multiple attaccos de Stokes-Adams occurrente intra un breve periodo de tempore, generalmente post que agentes sympathomimetic e vagolytic se habeva monstrate totalmente inefficace o solmente partialmente efficace. In plus, 12 casos de arresto cardiac occurrente durante operationes intracardiac esseva tractate con molar lactato de natrium intra variabile periodos post le arresto. Septe del patientes esseva resuscitate pro varie periodos de tempore, e 4 superviveva e quitava le hospital. In general, le usual mesuras therapeutic pro arresto cardiac habeva essite probate sin successo ante le administration de molar lactato de natrium.

Le presentia de extrasystoles in le electrocardiogramma preliminar es un contraindication del uso de lactato de natrium o al minus establi le necessitate de administrar le droga con alte grados de previdentia e sub le constante supervigilantia de observationes electrocardiographic. Augmento de pre-existente extrasystoles, breve paroxysmos de tachycardia ventricular, e le nove disveloppamento de extrasystoles ha essite observate. Congestive disfallimento cardiac es etiam un possibile effecto adverse de therapia a lactato de natrium. Ben que le effectos de molar lactato de natrium esseva simile in qualitate al effectos de bicarbonato de natrium, le prime de iste medicationes esseva alique plus efficace post prolongate periodos de tempore.

Comparationes preliminar con epinephrina e Isuprel suggere que in doses de comparabile efficacia e administrate sub comparabile conditiones, lactato de natrium es minus profibrillatori. Proque le principio de su action differe ab illo del action de drogas vagolytic e sympathomimetic, illo pote esser usate como supplemento de iste drogas e pote esser efficace in conditiones ubi illos es completamente inutile.

ACKNOWLEDGMENT

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CLINICAL PROGRESS

Digitalis and the Electrocardiogram

By ALFRED PICK, M.D.

THE action of digitalis and related glycosides is reflected in the electrocardiogram in a manifold fashion. Apart from altering the speed and mode of ventricular repolarization, represented by the ST-T portion, practically any type of disturbance in the formation or propagation of the cardiac impulse can result from digitalis medication; on the other hand some of these disorders of rhythm occurring spontaneously, may disappear on exhibition of the drug. Whether a *therapeutic* or a *toxic* effect will prevail, and the time until one or the other becomes manifest, depend on a number of variables and cannot be predicted in a given case. Whereas the dose and mode of administration can be adjusted according to estimated needs, other factors that may largely influence the outcome of therapy are more difficult to assess in a clinical evaluation of the individual patient. This difficulty refers to the complexity of electrolytic disorders associated with congestive heart failure, the condition of the myocardium, and the speed and extent to which the glycoside is absorbed, metabolized, and excreted. It is for this reason that each new digitalization, and determination of a maintenance dose, should be viewed as a therapeutic experiment at the bedside, the outcome of which is uncertain. The decision to continue or to interrupt medication, and in what manner to change the basic therapeutic plan, will depend largely on the electrocardiographic control of the early therapeutic results.

In table 1 the most common electrocardiographic manifestations of digitalis action are arranged from the viewpoint of their practical clinical significance, regardless of the various underlying physiologic mechanisms. Thus in

the first column are listed "therapeutic" effects, that is those alterations that may be considered as "safe" with regard to continuation of digitalization according to plan. These include deformation of the ST segment to a sagging appearance, lowering of the T wave, obvious or apparent shortening of the Q-T duration, and moderate depression of A-V conductivity causing prolongation of the P-R interval within the range of 0.20 to 0.30 second during sinus rhythm, and slowing of the ventricular rate—one of the spectacular effects of digitalis therapy—in rapid atrial arrhythmias (paroxysmal tachycardia, flutter, and fibrillation). Reduction of the ventricular rate under the latter circumstances may become so pronounced that a subsidiary pacemaker, usually one originating in the A-V node, may escape for 1 beat or for several successive ones. *Intermittent* A-V dissociation induced in this manner in atrial fibrillation should not preclude further digitalization, provided that the average ventricular rate is not less than 50 nor more than 70. Beyond these limits onset of *persistent* A-V dissociation (with very slow or very fast regular ventricular rates) can be expected, which requires a reduction of the digitalis dose applied.

Apart from reducing the ventricular rate in rapid ectopic atrial rhythms in this manner, digitalis may affect the abnormal atrial mechanism itself. When the response of cases with atrial tachycardia, flutter, or fibrillation is closely followed in the electrocardiogram, 2 seemingly contradictory effects can be observed. Usually the rapidity of the atrial deflections is enhanced, and the slower types (tachycardias and flutter) are converted, sooner or later, to the most rapid one—fibrillation. Often, however, particularly when digitalization is started soon after the onset of paroxysmal rapid heart action, atrial action slows, the abnormal mechanism is stopped, and sinus rhythm is restored. The background for this apparent paradoxical

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TABLE 1.—*Clinical Significance of Digitalis Effects on the Electrocardiogram*

Therapeutic	Excessive	Toxic
1. ST-T configuration 2. P-R prolongation 3. In atrial fibrillation: Ventricular slowing Nodal escape 4. In rapid atrial arrhythmias: tachycardia → flutter → fibrillation fibrillation → sinus rhythm	1. Sinus rhythm changed to: Atrial fibrillation or Atrial tachycardia with irregular ventricular response 2. Nodal tachycardia with A-V dis- sociation 3. S-A block → nodal rhythm with (delayed) retrograde conduc- tion → reciprocal beating 4. Second degree and complete A-V block	1. Bigeminy due to ventricular premature systoles 2. Ventricular premature sys oles in runs or multifocal 3. Ventricular paroxysmal ta hy- cardia (bidirectional) 4. Ventricular fibrillation
What to do about digitalis therapy		
CONTINUE	REDUCE	STOP

behavior of the atria on different occasions is the known double action of digitalis upon the atrial myocardium. By its direct action it tends to depress conductivity and to slow propagation of the rapid impulses; by its simultaneous indirect action, via the vagi, it tends to shorten the refractory phase of the atrial myocardium and thus to enhance its conductivity. Depending on the dominance of one or the other of these 2 effects, rapid atrial activity will either be stopped, or be maintained and augmented. This is one of the clinical situations when unpredictability of digitalis effects is exemplified clearly in the electrocardiogram. But, regardless of the outcome of such an experiment, the patient will benefit from it because the ventricular rate slows due either to restoration of sinus rhythm or depression of A-V conductivity accompanying acceleration of the atrial action.

In the second column of table 1, under the heading "excessive," are listed disorders of impulse conduction or formation, as well as their combinations, all of which, when induced by digitalis, require great caution in continuation of the medication because they may herald severe and dangerous stages of digitalis toxicity. With one exception, initiation of atrial fibrillation from pre-existent sinus rhythm, a rather rare event, they usually require an electrocardiogram to establish a proper diagnosis. This is pertinent, since some of these disorders have specific clinical significance. Thus it has been recognized recently¹ that an ectopic atrial tachycardia with irregular ventricular response may develop following doses of digi-

talisis ordinarily considered as therapeutic when the drug is employed in potassium-depleted states, e.g., subsequent to a massive diuresis. Less well known, but common in our own experience, is a complete A-V dissociation engendered not by A-V block, but by acceleration of the ordinarily subsidiary A-V nodal pacemaker (to rates between 70 and 100). When this occurs in the presence of atrial fibrillation, the regularization of the ventricular rhythm may be mistaken at the bedside for conversion to sinus rhythm.

Slowing of a sinus tachycardia by digitalis should be attributed to abatement of heart failure rather than to a direct action of the drug upon the primary pacemaker. When, during sinus rhythm, the ventricular rate drops below 50, development of an advanced conduction disturbance, usually involving the A-V junctional tissues, must be suspected and verified in the electrocardiogram. Irregular A-V conduction in sinus rhythm (second degree A-V block type I, i.e., with Wenckebach periods), and its progression to complete A-V dissociation with a slow ventricular rate, must be viewed as signs of digitalis excess. This block remains the main evidence of digitalis toxicity when the myocardium is unaffected by disease, e.g., when large amounts of digitalis are consumed accidentally by children, or in suicidal attempts by adults. When second degree A-V block develops after therapeutic doses in young persons with febrile conditions, the presence of an acute myocarditis is strongly suggested.

Among other types of conduction disturb-

ances, only S-A block is attributable to digitalis action; in fact, digitalis is its most common cause. Intraventricular block, on the other hand, is not a typical consequence of digitalis medication. On the contrary, its disappearance is frequently observed in the course of effective digitalization. S-A block with its long ventricular pauses leads to escape of subsidiary centers and thus to the establishment of slow nodal rhythms with A-V dissociation or with persistent retrograde conduction of the impulse to the atria. The latter may be associated with depression of A-V conductivity, likewise induced by digitalis, and then conditions are favorable for the development of reciprocal beating of the ventricles.

While all these disorders of rhythm must be considered to represent states close to digitalis toxicity, the need to discontinue the medication at once, under all circumstances, is not as strict as in the case of ectopic impulse formation in the ventricles. When heart failure is not severe, or partially controlled by the digitalis dose that produced the arrhythmia, it is best to interrupt the medication for a few days and to resume it with a reduced dose. When the condition of the patient is critical and the demand for therapy is acute, continuation of treatment is feasible as long as more severe signs of toxicity, (ventricular ectopic beats) do not show up in frequent electrocardiographic controls. It would appear that the combined administration of potassium and digitalis may be of value in keeping the patient at such "subtoxic" levels if there is great urgency for digitalis maintenance.

Listing of premature systoles and paroxysmal tachycardia of ventricular origin in the last column of table 1, under the heading of digitalis toxicity, does not imply that every patient revealing this type of arrhythmia should automatically be excluded from the benefits of digitalis therapy. Ventricular ectopic impulse formation may be a manifestation of myocardial pathology or of a failing heart and may disappear upon digitalis medication. However, when such ectopic beats develop soon after initiation of digitalis therapy or in the course of protracted medication, danger may be imminent and the medication must be stopped. If, as is sometimes the case, informa-

tion concerning preceding digitalization is unobtainable, the following electrocardiographic features are helpful in establishing the diagnosis of digitalis toxicity: (1) fixed coupling of premature beats of variable bizarre contour, resulting in ventricular bigeminy; (2) their multiplication in short runs; (3) a so-called bidirectional type of paroxysmal tachycardia; and (4), of course, other electrocardiographic changes attributable to digitalis action, such as the typical ST-T deformation and the various degrees of A-V block mentioned previously.

Premature ventricular systoles and ventricular tachycardia may be erroneously diagnosed when aberrant ventricular conduction has developed as a consequence of a rapid ventricular rate, e.g., in paroxysmal atrial fibrillation. The differential diagnosis² is of great practical importance since, in the latter case, intensification, and, in the former, interruption of digitalis medication is indicated. Admittedly, however, situations may arise where the diagnosis or exclusion of digitalis toxicity remains a matter of trial and error.

Ventricular fibrillation, the most advanced stage of digitalis intoxication is, fortunately, a rare event although it is known to occur precipitously on occasion in individuals particularly sensitive to the drug. In most cases it can be avoided by recognition of the premonitory signs noted above and their proper handling in time.

Bigeminy and associated signs of digitalis excess will disappear spontaneously once the medication has been stopped, but this may take some time, even weeks, during which the clinical condition may necessitate active treatment. Attacking digitalis-induced ectopic ventricular beats by quinidine or procaine amide is hazardous since, paradoxically, these 2 drugs may enhance rather than abolish the ectopic impulse formation under such circumstances (probably by creating conditions favorable for multiplication of a ventricular reentry mechanism). If the need for immediate control of the abnormal mechanism is great, intravenous injection of 20 ml. of magnesium sulfate (20 per cent) may transiently suppress the ectopic beats even in most advanced forms of toxicity. Impressive and long lasting effects

may be achieved by oral administration of potassium chloride, 2 to 3 Gm. every 3 to 4 hours. This agent too, however, has its pitfalls. It cannot be used when renal failure accompanies heart failure and, in our experience, it may counteract not only digitalis toxicity but also the therapeutic effects of the drug.

On an empirical clinical basis it would appear that some balance is necessary between digitalis and potassium concentrations in the organism in order to achieve an optimal therapeutic effect. A disturbance of this equilibrium in one or the other direction will lead to clinical and electrocardiographic signs of digitalis poisoning, or to failure of digitalis to act therapeutically. The optimal value of this "digitalis/potassium ratio" is unknown and perhaps varies from case to case. While at present, therefore, the simultaneous use of digitalis and potassium salts rests on uncertain empirical grounds, an approach to the solution of this vital clinical problem has been provided by recent investigations concerning the action of drugs and electrolytes upon the single myocardial cell.

Methods have been developed in several physiologic laboratories³⁻⁶ for introduction of a tiny glass electrode, 1μ or less in diameter, into the interior of a single myocardial fiber after piercing its membrane. Such experiments have been successfully carried out on excised cardiac tissues of various species and recently on the beating dog heart in situ. This method permits: (a) direct galvanometric measurement of the polarity and magnitude of potential differences across the cell membrane in its resting state; (b) recording of the magnitude and time course of alterations of these potential differences, when the cardiac cell undergoes excitation, either spontaneously by the propagated cardiac impulse or induced artificially by electric or other extraneous stimuli; (c) correlation of these bioelectric events with the ionic equilibrium and ionic transfer across the membrane during rest and activity; (d) investigation of influences exerted upon membrane resting and action potentials by changes in cellular environments, by nervous influences, and by various drugs; and (e) comparison of the electrophysiologic behavior of skeletal and cardiac muscle, on the one hand, and between specific

cardiac fibers and ordinary atrial and ventricular fibers, on the other. Thus, a completely new field has been opened for investigation of cardiac physiology under normal and abnormal conditions, the limits of which cannot be foreseen as yet. Some of the present knowledge gained in this manner^{6,7} is illustrated in diagrammatic form in figures 1 to 3.

Figure 1 shows a schematic diagram correlating the time course of ionic exchange (A) with bioelectric events (B) at the cell membrane during activation and deactivation of a single myocardial (ventricular) fiber, and their temporal relationship to the surface electrogram of the ventricle (C).

In A, the distance between the 2 pointed vertical bars indicates the time during which the tip of a capillary electrode was kept within a ventricular fiber after piercing its membrane, which is represented by the shaded and stippled areas; the former represent the resting state of the fiber, the latter a state of activity engendered by the propagated cardiac impulse. The symbols Na^+ and K^+ indicate accumulation of sodium and potassium ions at respective sides of the resting membrane; their exchange across the membrane during activity is indicated by arrows.

In B, the horizontal line at 0 represents zero potential recorded by a galvanometer connected to a capillary electrode kept at the surface of the cell. Upon piercing of the cell

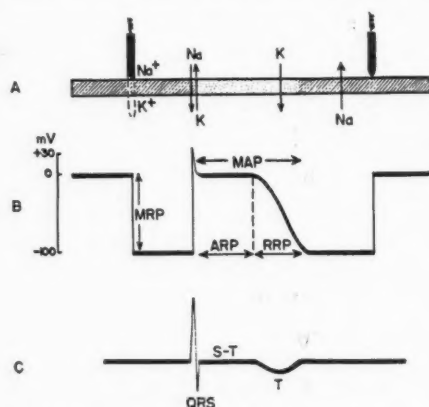


FIG. 1. Events at the cell membrane during cycle of activation and deactivation of a single myocardial fiber.

membrane a negative deflection of about 100 mv. magnitude is recorded—the membrane resting potential (*MRP*). *MRP* remains at a constant (negative) level until the cell is reached by the activation process. The latter is indicated by a rapid reversal of the galvanometric deflection to above zero, the positive overshoot, with subsequent stabilization at zero during the major part of cellular activity. Return to the resting state takes place gradually as indicated by the downward slope of the galvanometric deflection to the negative resting level. The time between positive overshoot and complete return to the resting state represents the duration of the membrane action potential (*MAP*). From its onset to the beginning of its decline the cell is totally unresponsive to external stimuli—it is in its absolute refractory phase (*ARP*); during the time of decline of *MAP* the cell becomes gradually more and more responsive to strong stimuli—it is in its relative refractory phase (*RRP*).

C represents the QRS and (inverted) T deflection of an unipolar electrogram recorded from the surface of the ventricle simultaneously with *MRP*.

According to the present state of knowledge the events depicted in *A*, *B*, and *C* appear to be coupled in the following manner: Arrival of the activation process at the cell causes an abrupt change in the permeability of its membrane to sodium and potassium ions. Consequently sodium enters the cell and this causes the almost instantaneous reversal of the negative transmembrane potential (*MRP*) to a positive overshoot, synchronous with the upstroke of R in the surface electrogram. Subsequent exit of potassium ions from the cell interior abolishes the positive spike and stabilizes *MAP* at zero levels, 2 events reflected in the surface electrogram as the remainder of the QRS deflection and the isoelectric ST segment respectively. Slow return of potassium ions into the cell signifies restitution of the state of inactivity, the tardiness of the process being reflected in the gradual decline of *MAP* and the broadness of the T deflection, all this being completed at the same time. Return of sodium ions to the cell surface appears to be accomplished during the resting ("diastolic") phase of this cycle.

The forces that keep potassium ions outside the cell during cellular activity and cause extrusion of sodium ions during the resting period are unknown and are presently ascribed to some active metabolic processes of the membrane itself to which the term "sodium and potassium pumps" have been applied.

In figure 2 are shown membrane resting and action potentials of various types of muscle tissue:⁶ (*A*) dog ventricle, (*B*) dog atrium, (*C*) rat diaphragm, (*D*) Purkinje fiber of the kid. Differences in duration and steepness in the downstroke correspond to differences in the duration of the refractory period of ventricular, atrial, and skeletal muscle. In the Purkinje fiber (*D*), pacemaker activity is represented by spontaneous recurrence of the positive spike at a rate of 30 per minute. Note that, in contrast to the other muscle fibers (*A*, *B*, *C*), the membrane resting potential does not remain at a constant level but declines from -100 to -60 mv. between successive spikes. This gradual loss of negative charge of the cell interior, referred to as "prepotential," appears to be characteristic of specific cardiac tissue and is probably related to its pacemaker function. Following treatment by digitalis preparations as demonstrated in the frog heart,⁸ the ventricular membrane action potential (*A*) changes in contour and duration and becomes progressively more like that of atrial and skeletal muscle (*B* and *C*).

In figure 3 are listed various factors that act at cellular levels, as demonstrated experimen-

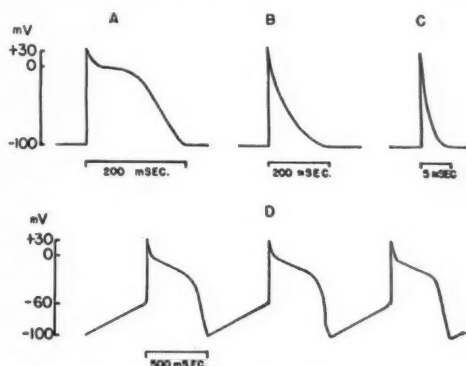


FIG. 2. Membrane potentials of various types of muscle tissue.

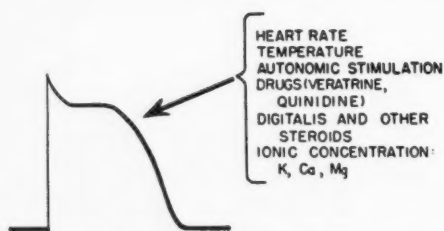


FIG. 3. Various factors that alter the membrane resting and action potentials.

tally by alterations in the shape, duration, and amplitude of the various phases of membrane resting and action potentials (*MRP* and *MAP*).

What then is the bearing of this recent progress achieved in the laboratory on the understanding of the variety of digitalis effects in the electrocardiogram? From the information at hand, it is as yet not possible to draw conclusions about mechanisms of the numerous arrhythmias representing the electrocardiographic evidence of therapeutic and toxic actions of digitalis. However, it has been demonstrated conclusively⁸ that digitalis preparations produce characteristic alterations in the shape and the duration of the membrane action potential in the frog heart. These alterations appear to be similar, or opposite, to those occurring in membrane action potentials of mammalian papillary muscle or Purkinje tissue subsequent to changes in the ionic concentration of the extracellular fluid, in particular of the K/Ca relationship. On this basis one could expect some differences in the response of the cardiac cell to digitalis, when the latter is applied to preparations surrounded by fluid that is either depleted or enriched in its potassium content. Although experiments designed specifically in this direction have not been reported thus far, it is hoped that a proper evaluation of the digitalis/potassium relationship at cellular levels may provide the basis

for a new rationale in the clinical use of the digitalis drugs. Some of the puzzles and hazards associated with digitalis therapy of present days may thus be eliminated in the future.

SUMMARY

The various effects of digitalis upon the electrocardiogram are reviewed and grouped with regard to their clinical significance. The ap-
peutic or toxic actions of digitalis seem to depend on as yet poorly understood relationships to potassium metabolism. An insight into this relationship might be gained in the future in view of recent developments in the field of cardiac electrophysiology.

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ABSTRACTS

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ATHEROSCLEROSIS

Adlersberg, D., Stricker, J., and Himes, H.: Hazard of Corticotropin and Cortisone Therapy in Patients with Hypercholesterolemia. *J. A. M. A.* **159**: 1731 (Dec. 31), 1955. Abstracted, *Circulation* **15**: 441 (Mar.), 1957.

Joyner, C., Jr., and Kuo, P. T.: The effect of Sitorol Administration upon the Serum Cholesterol Level and Lipoprotein Pattern. *Am. J. M. Sc.* **230**: 630 (Dec.), 1955. Abstracted, *Circulation* **15**: 404 (Mar.), 1957.

Hewitt, J. E., and Hayes, T. L.: X-Irradiation and Lipoprotein Metabolism in Various Species. *Am. J. Physiol.* **185**: 257 (May), 1956.

In the rabbit low-density lipoproteins were increased 30 hours after X-ray irradiation. Ten to 13 days after dogs were irradiated, the 2 lower density classes were observed to be increased in concentration. However, the highest density class is decreased in this species. In the rat high-density lipoproteins exhibit an increased concentration 3 days after irradiation. On the other hand, the lower density lipoproteins were increased after 8 days in this test object. Mice had a marked decrease in concentration of high-density lipoproteins at 4 days. Hyperlipoproteinemia and higher average flotation rates for lipoprotein molecules went together. This indicated that metabolism of lipids in the irradiated animal were also altered qualitatively. In the preagonal period low-density lipoproteins were markedly increased in rabbit, rat, and dog.

OPPENHEIMER

Bilinski, B. V.: Pathogenesis of Atherosclerosis. *Klin. med.* **34**/4: 13 (Apr.), 1956.

In 111 apparently normal persons the blood cholesterol exceeded 300 mg. per cent in 3.6 per

cent of the cases, especially in middle-aged persons of the hypersthenic body build. In 106 hypertensive subjects this percentage was 24.3 per cent, in 117 hypertensive persons with signs of atherosclerosis it was 58.2 per cent, and in 109 nonhypertensive persons with atherosclerosis it was 58.2 per cent. In all persons who showed regression or fibrous modification of atherosclerotic changes at autopsy, cholesterol was normal shortly before death. All persons who had definitely elevated values (and usually low lecithin-cholesterol ratios) showed progressive atherosclerosis with fresh deposits at autopsy. Some who had progressive changes had low values of cholesterol before death, but in these persons circulatory failure was present, which cause cholesterol values to fall. In persons with atherosclerosis and especially in hypertensives the day-by-day fluctuations of cholesterol values are much greater than in normal subjects. Persons whose food was high in lipids usually had signs of progressive atherosclerosis at autopsy, while those whose food was low in lipids usually showed the regressive or fibrous phase of atherosclerosis. On the basis of these observations, the importance of early recognition of hypercholesterolemia and its early dietary treatment is stressed.

LEPESCHKIN

Herbst, F. S. M., Leven, W. F., and Waddell, W. R.: Effects of Intravenously Administered Fat on the Serum Lipoproteins. *Science* **123**: 843 (May), 1956.

Electrophoretic analyses of serum were performed in 8 normal human subjects and in an equal number of dogs before and after an intravenous infusion of emulsified fat. The material consisted of 50 Gm. of cottonseed oil (or 50 Gm. of synthetic triolein) with added soybean phosphatide.

The changes in lipoproteins and globulins seen on

paper electrophoresis were identical with those induced by the intravenous administration of heparin during alimentary hyperlipemia in normal subjects and in patients with idiopathic hyperlipemia.

Heparin apparently activates a lipoprotein lipase, known as "clearing factor." It is not known whether an infusion of fat emulsion acts by a similar or different mechanism.

WAIFE

Prior, J. T., and Hartmann, W. H.: The Effect of Hypercholesterolemia upon Intimal Repair of the Aorta of the Rabbit Following Experimental Trauma. *Am. J. Pathology* **32**: 417 (May-June), 1956.

Trauma to the intimal surface of the aortas in young rabbits fed high-cholesterol diets was mechanically produced. Lesions in the aortas of sacrificed animals were studied and evolution of atherosclerotic plaques observed. Within 14 days of injury a plaque composed of lipids and scar tissue was formed, histologically identical with early atherosclerotic plaques in human beings. Twenty days later these induced lesions showed necrosis and inhibition of connective tissue development. It is postulated that there is an inhibitory effect of cholesterol upon connective tissue repair.

HARVEY

LeRoy, G. V.: Studies of Cholesterol Synthesis in Man Using Carbon Labeled Acetate. *Ann. Int. Med.* **44**: 524 (Mar.), 1956.

Cholesterol is an important constituent of the body. The relationship between cholesterol and atherosclerosis is of great contemporary interest. Our interest in cholesterol is related to the metabolic fate of acetate, the latter being the precursor in the biosynthesis of cholesterol in mammals. We have found that there is a very rapid interchange between the free cholesterol of the liver and that of the plasma, so that the liver plasma system can be considered as 1 large rapidly exchanging compartment. It seems proper to include the cholesterol passing through the enterohepatic circuit in this compartment. The size of the pool of rapidly exchanging cholesterol ranges from 20 to 30 Gm. and has an average turnover time of from 8 to 12 days. The body therefore utilizes from 2 to 3 Gm. per day, of which the smaller fraction may come from the diet. On the basis of this estimate, the major source of new cholesterol in man is believed to be hepatic synthesis, which appears to contribute on the average 2 or more Gm. per day of newly formed cholesterol. When acetate is given intravenously, we have found that approximately 1 per cent is converted to cholesterol. Most of this synthesis appears to be completed rapidly, probably within the first 2 to 4 hours. During the same period of time approximately one third of the radiocarbon appears in expired air as carbon dioxide. The balance of the acetate is widely dis-

tributed in many compounds, including fatty acids, amino acids, nucleic acid units and the like. These studies illustrate in a very comprehensive manner a practical technic for the study of many aspects of cholesterol metabolism in man. The dose of radiocarbon is well within the permissible limit, so that repeated tests can be performed.

WENDKOS

CONGENITAL ANOMALIES

Hickie, J. B., Gimlette, T. M. D., and Bacon, A. P. C.: Anomalous Pulmonary Venous Drainage. *Brit. Heart J.* **18**: 365 (May), 1956.

The authors describe the features of 13 patients over 10 years of age with partial anomalous venous drainage. Right anomalous veins were present in 12 and left in 2. Nine had an atrial septal defect; 3 had a left superior vena cava; 1 pulmonary stenosis; 2 mitral stenosis and 1 an abnormality of the Eustachian valve.

The fundamental disturbance is similar to an atrial septal defect, that is, recirculation of oxygenated blood through the lungs. Ultimately, enlargement of the right atrium and right ventricle and raised pulmonary arterial and right ventricular pressures occur. Symptoms probably do not arise unless the anomalous drainage is 50 per cent or more of the pulmonary flow.

A clinical differentiation between anomalous pulmonary venous drainage and atrial septal defect is not possible. The majority of patients are asymptomatic for years. Symptoms may be progressive dyspnea, recurrent bronchitis, hemoptysis, precordial pain, giddiness, and palpitation. Central cyanosis was present in half of the patients. The signs of increased pulmonary flow may be present.

The electrocardiographic signs were likewise that of atrial septal defect. The P waves may be bifid or peaked. The QRS complex is always abnormal. Either right bundle-branch block or right ventricular hypertrophy was present. Atrial arrhythmias are common. The cardiac silhouette is similar to other types of left to right shunts.

A homogeneous pulsating bulge is seen to the left of the upper mediastinum when the anomalous veins enter a persistent left superior vena cava draining into the left innominate vein. The normal superior vena cava may also dilate and pulsate. These 2 bulges form the characteristic "figure eight."

A comma-shaped shadow may be seen parallel to the cardiac border, which disappears into the cardiophrenic angle when the anomalous veins drain into the superior or inferior vena cava.

Nevertheless, none of the authors' cases was suspected of having anomalous venous drainage from the radiologic study.

Cardiac catheterization is of diagnostic value. The catheter may pass into a pulmonary vein. If not, the diagnosis is established by determination of

the oxygen content of the blood in the right atrium and that in the venae cavae and innominate vein. The diagnosis can be inferred when the blood samples show evidence of a shunt into the right atrium and one of the great veins.

Oye-dilution curves are diagnostic of a left-to-right shunt but not specific for anomalous pulmonary venous drainage.

SOLOFF

Downing, D. F., and Goldberg, H.: Cardiac Septal Defects. I. Ventricular Septal Defect. Analysis of One Hundred Cases Studies During Life. *Dis. Chest* 29: 475 (May), 1956.

Certain data collected in the course of study of 160 consecutive patients with ventricular septal defect in whom right heart catheterization was performed were presented. Although the malformation has been thought to be of little significance, the authors' observations indicated that it is of serious import. The majority of patients had symptoms. Fatigue and shortness of breath were the most common. Cough and syncope occurred. Cyanosis at some time appeared in many. Cardiac failure may be expected in approximately 20 per cent and occurred relatively early in life in a large number. Roentgen and electrocardiographic abnormalities were the rule. The majority of individuals showed, on roentgenographic examination, increased prominence of peripheral pulmonary vascular markings, dilatation of the main pulmonary artery, cardiac enlargement to the left with rounding of the left border, and prominence of the right ventricle in the right anterior oblique view. The electrocardiogram showed definite or suggestive evidence of right ventricular hypertrophy in 59 per cent of the patients. Conduction defects were occasionally seen. In this series, the character of the murmur and its location varied greatly. A systolic murmur was heard in 98 patients, and in the majority was best heard at some point along the left sternal border. A diastolic murmur was heard in 18 subjects (17 in combination with the systolic and in one as the sole murmur. One patient had no murmur). In those in whom the diastolic murmur was heard along the left sternal border, it was thought probably due to pulmonary insufficiency. Pulmonary hypertension was present in a large number of the patients. It was believed that the large pulmonary flow resulted in functional contraction of the small pulmonary vessels. This results in increased resistance to flow and increased pulmonary pressure. Anatomic changes develop to further increase resistance. The direction of flow through the defect thus may change and a constant right-to-left shunt ensue. This is the natural history of those patients who are classified as having the Eisenmenger complex, a term which these authors thought should be abandoned.

The symptoms, physical findings, roentgenographic, and electrocardiographic signs of inter-

ventricular septal defect are not characteristic. Diagnosis depends upon cardiac catheterization, supplemented in certain cases by contrast radiography.

MAXWELL

Ingalls, T. H.: Causes and Prevention of Developmental Defects. *J.A.M.A.* 161: 1047 (July 14), 1956.

Congenital defects are not all genetically determined at the moment of conception; many are acquired during the ensuing fetal development. Research done at the Harvard School of Public Health during the past decade indicates that most congenital anomalies originate as fetal manifestations of critical distress in pregnancy. These acquired defects have been studied in the gravid mouse by using hypoxia as a standard stress at different stages in gestation. Hypoxia results in a whole panorama of deviations determined as to kind and severity by the timing and degree of the stress applied to the mother. It appears that partial control of congenital anomalies can be effected by using on a combined front the 3-fold forces of laboratory, clinical, and epidemiologic methodologies. The field of acquired congenital anomalies emerges as of equal stature with genetics itself; it surpasses genetics in its promise as an applied science in the problems of congenital defects in man.

KITCHELL

Hollendonner, W. J., and Pastor, B. H.: Dextro-position of the Heart Simulating Congenital Dextrocardia. *Am. J. Med.* 20: 647 (April), 1956.

A case of marked cardiac displacement due to eversion of the diaphragm, with the roentgen appearance of dextrocardia, is presented. Displacement of the heart (dextroposition) may simulate congenital dextrocardia or incomplete rotation of the heart (dextroversion). Differentiation of these conditions, although difficult, may be of considerable clinical importance. True congenital dextrocardia can be identified by means of the pathognomonic electrocardiographic pattern. Congenital dextroversion may be difficult to differentiate from dextroposition except by identification of the factor or factors producing the displacement of the heart.

HARRIS

Michel, D., and Herbst, M.: The Diagnostic Value of Decholin Injection through the Cardiac Catheter. *Ztschr. Kreislaufforsch.* 45: 110 (Feb.), 1956.

An interval of less than 5 seconds between rapid injection of 3 to 5 ml. of a 10 per cent solution of Decholin into the right ventricle and the sensation of bitter taste indicates a right-to-left shunt with certainty. In Fallot's trilogy this short circulation time is present only after injection into the right atrium, while in tetralogy it is present also after injection into the right ventricle. This test is never

accompanied by any side effects such as appear during the ether test.

LEPESCHKIN

CORONARY ARTERY DISEASE

Keys, J. R., Dry, T. J., Walters, W., and Gage, R. P.: Cholecystectomy in Patients with Coronary Heart Disease. *Proc. Staff. Meet., Mayo Clin.* **30:** 587 (Dec.), 1955. Abstracted, *Circulation* **15:** 202 (Feb.), 1957.

Weiss, M. M.: Ten Year Prognosis of Acute Myocardial Infarction. *Am. J. M. Sc.* **231:** 9 (Jan.), 1956. Abstracted, *Circulation* **15:** 460 (Mar.), 1957.

Saphir, O., Ohringer, L., and Silverstone, H.: Coronary Arteriosclerotic Heart Disease in the Younger Age Group: Its Greater Frequency in this Group Among an Increasingly Older Necropsy Population. *Am. J. M. Sc.* **231:** 494 (May), 1956.

The necropsy material on patients over 20 years of age covering a 34-year period was studied to determine whether or not arteriosclerotic heart disease (AHD) has occurred in the younger age group more frequently in recent years than 2 decades ago. It was found that the total incidence of the disease has not changed during the period of study. The preponderance of males over females was striking; there were 1403 males and 762 females in the total group. The number of patients with AHD under 50 years of age was 7.3 per cent in 1920 to 1929 compared to 12.2 per cent from 1940 to 1949 and 11.5 per cent from 1950 to 1953. While there is an increase in all age classes under 50 years, the most striking increase in frequency of AHD occurred between the ages of 40 to 50. During the same period the necropsy population has become increasingly older. In speculating about the factors involved in the increase in AHD in younger age groups the authors allude to the rise in consumption of dietary fats. However, since AHD among the total necropsy population has not changed, factors other than diet may be responsible for the increase in younger groups.

SHUMAN

Fulton, W. F. M.: Chronic Generalized Myocardial Ischemia with Advanced Coronary Artery Disease. *Brit. Heart J.* **18:** 341 (May), 1956.

The author described 4 cases that are part of a series of 26 with advanced coronary artery disease that have been studied after injection of the coronary arteries with a radiopaque medium followed by stereoradiography of the intact and of the partially dissected heart. Clinically, these patients corresponded to recurrent acute coronary insufficiency of many years' duration.

Each case had advanced coronary artery disease.

The coronary ostia were narrow. No case had recent or old myocardial infarction in the regions of the narrowed or occluded arteries.

Fibrosis of the diffuse patchy type was confined mainly to the inner zone of the left ventricle but spared the immediate subendocardial layer. It is in this zone that the arteriograms show a network of dilated intercommunicating channels.

Myocardial ischemia insufficient to produce massive structural damage is the stimulus for the formation of these collateral vessels. Because the inflow of blood to the myocardium is reduced at its source, these internal rearrangements of channels of supply can at best achieve only a more uniform distribution of poverty. The least favorably situated region, which is the inner zone of the left ventricle, being farther from the source of blood supply, suffers first and undergoes focal necrosis with resultant patchy fibrosis.

SOLOFF

Pollock, C. B. E.: The Early Management of Myocardial Infarction. *J.A.M.A.* **161:** 404 (June 2), 1956.

The patient in the acute stage of myocardial infarction needs rest, reassurance, and relief from pain. Morphine is the preferred agent for pain relief. Depending on conditions, the patient may also need hospitalization, oxygen therapy, anticoagulant therapy, coronary vasodilators, special nursing care, and particular attention to diet and elimination. Complications to be feared during the first few days after the acute infarction include shock, pulmonary edema, cardiac arrhythmia, extension of infarction, embolism from mural thrombosis, pericarditis, and congestive heart failure. Shock requires early recognition and treatment. Pulmonary edema requires prompt and vigorous therapy, including morphine administration, elevated position of the upper part of the body, trapping of blood in the extremities, and administration of oxygen. Although rapid digitalization and use of aminophylline may be harmful theoretically, practically they continue to be useful and sometimes essential measures. Atrial arrhythmias are usually best controlled by digitalization. Ventricular irritability calls for the administration of suppressive medication such as quinidine or procainamide. When one is dealing with ventricular paroxysmal tachycardia, the slow intravenous injection of procainamide under electrocardiographic control is probably the method of choice, or intramuscular use of appropriate quinidine preparations may be resorted to. Adequate anticoagulant therapy may prevent mural thrombosis in the left ventricle with subsequent embolism and peripheral venous thrombosis with embolism. Congestive heart failure requires the usual treatment for such failure, digitalization, salt restriction, and the use of diuretic drugs. Combinations of complications gravely increase the prognosis and call for careful and adept

combinations of therapy. This is particularly so when combinations of shock, ventricular arrhythmias, and pulmonary edema occur.

KITCHELL

Donney, J. L., McAuley, C. B., Martin, H. E., Ware, A. G., and Segalove, M.: Evaluation of the Serum Glutamic Oxalacetic Aminopherase (Transaminase) Test. *J.A.M.A.* **161**: 614 (June 16), 1956.

Serum aminopherase levels were determined in 77 patients with the unequivocal diagnosis of myocardial infarction and were compared with the levels found in 73 patients with other diseases. A serum aminopherase level of 40 units was selected as the dividing line between normal and abnormal. It was found that serial determinations were necessary as the rise in level might be transient. Return to normal could occur within 36 hours although it might remain elevated as long as 14 days; usually falls to normal levels occurred in 3 to 5 days. The height of the serum aminopherase level appears to bear a rough clinical correlation to the severity of infarction. Three false-negative results were found in patients with unequivocal myocardial infarction, an incidence reported as 4.75 per cent. False-positive results were found in some cases of liver disease, jaundice, acute pancreatitis, and pulmonary embolism. This test appears to have a definite place in the diagnosis of acute myocardial infarction. However, more study is needed in the equivocal categories.

KITCHELL

Judson, W. E., and Hollander, W.: The Effects of Insulin-Induced Hypoglycemia in Patients with Angina Pectoris before and after Hexamethonium. *Am. Heart J.* **52**: 198 (Aug.), 1956.

Eleven patients with hypertensive cardiovascular and/or coronary artery disease with angina pectoris and positive 2-step exercise tolerance tests (electrocardiographically and symptomatically) were used for the study. Eighteen insulin tolerance tests were performed on the 11 patients. Hexamethonium was given in a dose such that it produced postural hypotension and abolition of the hypertensive overshoot of the brachial pressure pulse to the Valsalva maneuver. Insulin-induced hypoglycemia failed to precipitate angina pectoris. Electrocardiographic changes occurred during hypoglycemia and were related to the reductions in the blood glucose and serum potassium concentrations. They were unlike the electrocardiographic changes observed during exercise-induced angina pectoris. Pretreatment with intravenous hexamethonium did not consistently alter symptoms, the response of the blood glucose, serum electrolytes, and the electrocardiogram to intravenous insulin. The experimental observations suggest that the dangers from insulin-induced hypo-

glycemia in patients with coronary artery disease may, on occasion, have been overemphasized.

RINZLER

Wroblewski, F., Rueggsegger, P., and LaDue, J. S.: Serum Lactic Dehydrogenase Activity in Acute Transmural Myocardial Infarction. *Science* **123**: 1122 (June 22), 1956.

It has recently been shown that glutamic oxaloacetic transaminase is released from cardiac muscle during experimental and clinical transmural myocardial infarction. In this report the authors record their studies on another enzyme, lactic dehydrogenase. The serum level was found to be elevated in leukemia and carcinomatosis as well as in acute transmural infarction. Normal values were found in pulmonary infarction, febrile diseases, and anemia.

The serum lactic dehydrogenase activity rises within 24 hours in experimental and human myocardial infarction and returns to the normal range within 5 to 6 days. Presumably the elevated levels result from the release of the enzyme from the infarcted muscle tissue. Further studies will be needed to determine the diagnostic or prognostic significance of this finding.

WAIFE

PHYSICAL SIGNS AND DIAGNOSTIC TECHNIQS

Guerin, J.: An Empirical Method for Cardiac Resuscitation during the Syncope of Stokes-Adams Disease. *Arch. mal. coeur* **48**: 1182 (Dec.), 1955. Abstracted, *Circulation* **15**: 413 (Mar.), 1957.

Manson, G., and Rindskopf, W.: Bilateral Adolescent Mammopathy as a Presenting Symptom of Rhabdomyosarcoma of the Heart. *J. Pediat.* **48**: 202 (Feb.), 1956.

A case report is presented of a 12-year-old girl who presented with bilateral breast masses, which on biopsy were found to be a tumor of sarcomatous type, but whose origin was undetermined. Following this, evidence of widespread metastatic disease appeared and death followed within 4 months. At autopsy, the tumor was found to be a rhabdomyosarcoma arising in the heart. The literature on the subject is reviewed.

HARVEY

Clark, E. C., and Bailey, A. A.: Neurological and Psychiatric Signs Associated with Systemic Lupus Erythematosus. *J. A. M. A.* **160**: 455 (Feb. 11), 1956.

The authors base their present report on a review of clinical records in 100 cases of clinically diagnosed systemic lupus erythematosus taken without selection from the files of the Mayo Clinic. The cases were observed in the years 1948 and through a part of 1951. Evidently this disseminated

disease can be accompanied by severe manifestations of both neurologic and psychiatric dysfunction. These can occur alone or in combination and are of the greatest diversity. Of these 100 cases, 28 showed signs or symptoms of neuropsychiatric disorder (17 of the 28 had evidence of psychic disturbance and 24 of 28 had neurologic dysfunction). It is concluded that clinical evidence of transient or permanent involvement of any part of the nervous system may appear during the course of systemic lupus erythematosus.

KITCHELL

Dittrich, W.: The Variability of the Interval between the Components of the Reduplicated Second Heart Sound in Mitral Stenosis. *Ztschr. Kreislaufforsch.* 45: 120 (Feb.), 1956.

In 17 cases of mitral stenosis with normal sinus rhythm the interval from the beginning of the second heart sound to the beginning of the opening snap of the mitral valve increased from about 0.04 sec. at R-R of 0.06 sec., to 0.11 sec. at R-R of 1.8 sec. Above R-R of about 1.1 sec., the interval showed comparatively little change. The same relations were present in 13 cases of mitral stenosis with atrial fibrillation; the dependence on R-R in each case was clear, but the dispersion of values for different cases at a given R-R was as much as 0.06 sec. Also, for a given preceding pause the values of the interval were greater. This may be due to the influence not only of the preceding pause but also of the pause preceding this, on the interval in question. After a long diastolic pause the left atrial pressure is lower and the opening snap, which occurs as soon as the left intraventricular pressure becomes less than the atrial pressure, accordingly takes place later. At a given heart rate the interval was shorter in cases with long duration of symptoms and with associated mitral regurgitation, but longer in those with hypertension (which causes anticipation of the second sound) and additional aortic regurgitation (which delays the fall of left ventricular pressure at the end of systole). No relation was found to the age and sex of the patient or to the presence of heart failure. After mild exercise the interval became shorter, whereas after mitral valvulotomy it became considerably longer. In cases with long P-R intervals (which facilitate emptying of the atrium) the interval was longer.

LEPESCHKIN

Haserick, J. R.: Evaluation of Three Diagnostic Procedures for Systemic Lupus Erythematosus. *Ann. Int. Med.* 44: 497 (Mar.), 1956.

Three methods for inducing the LE phenomenon were compared for sensitivity, accuracy, facility, availability of controls and the occurrence of false-positive and false-negative results. These methods were (1) heparinized bone marrow aspirated from the patient, (2) heparinized and clotted peripheral

blood, (3) a mixture of plasma from the patient and normal bone marrow from a dog. All 3 procedures were positive in classic examples of severe systemic lupus erythematosus, except for occasional false-negative results in the patient's own bone marrow procedure. (This was due presumably to the occasional hypoplastic marrows associated with the disease.) The differences between the 3 LE tests were more apparent in patients with low grade illness, or the so-called "lupus diathesis." In this group the peripheral blood LE test (clotted) was the most sensitive, the patient's own marrow LE test the next, and the plasma-dog bone marrow LE test the least sensitive. Of 33 such patients followed up to 3 years, all were living, suggesting that a weak positive LE test by itself is not necessarily of serious prognostic importance. A survey was made of 20 hematologists, selected by geographic location as well as because of a special interest in the LE phenomenon. In general, these authorities found the LE tests to be specific. False-negative LE tests were not infrequent in the face of typical systemic lupus erythematosus, but false-positive LE tests, such as in penicillin sensitivity, were rare. Positive LE tests in Apresoline reactors were not considered to be "false-positive," due to the close clinical resemblance with systemic lupus erythematosus. The clotted peripheral blood LE test and the plasma-bone marrow LE test were found to have special advantages. A combination of both is suggested as a practical office procedure.

WENDKOS

Tyler, D. E.: The Relationship between the Pressure Sustained by the Various Cardiac Valves and the Relative Frequency of Their Involvement in Rheumatic Fever. *Am. Heart J.* 51: 415 (Mar.), 1956.

The author has collected data with reference to the distribution of rheumatic valvular lesions and the pressures sustained by the various valves during the cardiac cycle. The incidence of rheumatic lesions of the valves in terms of frequency are as follows: mitral, aortic, tricuspid, and pulmonary. The pressures on these valves in terms of height in mm. Hg are in the same order, that is, the highest at the mitral and the lowest at the pulmonary valve. Distribution of rheumatic valvular lesions, therefore, follows the same pattern and is approximately proportional to the particular pressure sustained by each of the valves.

RINZLER

RHEUMATIC FEVER

Taranta, A., and Stollerman, G. H.: The Relationship of Sydenham's Chorea to Infection with Group A Streptococci. *Am. J. Med.* 20: 170 (Feb.), 1956.

Fifty-one patients with pure chorea were studied to determine the relationship between chorea minor and streptococcal infections. The incidence of ele-

valent streptococcal antibody titers, indicative of recent streptococcal infections, was higher in a group of 30 patients studied within 1 month from the onset of chorea (73.3 per cent) than in patients studied later (45.4 per cent). This incidence was lower than in a comparable group of patients with other manifestations of rheumatic fever (95 per cent). An analysis of the histories of 55 patients with chorea and other manifestations of rheumatic fever showed that the onset of chorea usually follows the onset of the other rheumatic manifestations. A longer lag period between streptococcal infections and chorea minor than between streptococcal infections and the other most common manifestations of rheumatic fever was suggested by these studies. The interpretation is advanced that the relatively long lag period between streptococcal infections and chorea may explain the lack of immunologic evidence of recent streptococcal infections in some cases of pure chorea. Immunologic studies of the cerebrospinal fluid in 15 patients with chorea failed to yield information on the pathogenesis of the disease.

HARRIS

Stollerman, G. H., Lewis, A. J., Schultz, I., and Taranta, A.: Relationship of Immune Response to Group A Streptococci to the Course of Acute, Chronic and Recurrent Rheumatic Fever. Am. J. Med. 20: 163 (Feb.), 1956.

Studying the clinical course of rheumatic fever in relation to streptococcal infection in 580 patients, the authors found a high initial titer of antistreptolysin O, antistreptokinase or antihyaluronidase in the sera of 95 per cent of patients examined within the first 2 months of onset of the rheumatic attack. The rate of fall of these 3 antibodies was unrelated to the subsequent clinical course of the rheumatic attack. Following suppressive therapy with aspirin or cortisone, all frank relapses of the disease unassociated with new streptococcal infections occurred within 2 months. Thereafter, the reappearance of frank rheumatic fever was invariably associated with immunologic evidence of new streptococcal infection. In the absence of new streptococcal infection the active rheumatic process appeared to be clinically arrested within 6 months of its onset in 95.7 per cent of the 580 patients studied.

The authors regard the 2 months following termination of a course of treatment with aspirin or cortisone (usually administered for 6 to 12 weeks) as the critical period required to observe the patient for signs or symptoms of a spontaneous relapse of the disease. After this interval, and providing that successful continuous chemoprophylaxis against new streptococcal infection is maintained, and adequate recovery of cardiac reserve has been gained, it has been found safe to return patients

to normal community life with little fear of clinical relapse.

The rate of fall of the antibodies may serve as a guide to the efficiency of antistreptococcal prophylactic measures maintained in rheumatic subjects to prevent recurrences of the disease. Continuous prophylaxis with antibiotics by current methods and the use of the antibody measurements employed in this study may make it possible to evaluate the natural history of rheumatic fever and rheumatic heart disease with reasonable assurance that the factor of intercurrent streptococcal infection has been excluded.

HARRIS

Hecht, M. S., Sheldon, W. E., Nolke, A., Hofstra, D., and West, E.: Results of Cortisone and ACTH Treatment of Rheumatic Fever. J. Pediat. 48: 300 (Mar.), 1956.

One hundred forty-one children with acute rheumatism and carditis were treated with cortisone or ACTH at the Children's Hospital in Detroit between 1950 and 1953. The results of therapy were contrasted with those obtained with another group of 114 children treated with salicylates between 1946 and 1950.

The hormone-treated patients were hospitalized, maintained on low-salt diets, given prophylactic penicillin during the hospital stay, and examined twice daily. Such an excellent treatment regimen was not followed in the salicylate control group. The results of the hormonal treatment compared to control treatment showed the death rate decreased by 50 per cent, which was not, however, significant. The reversal of physical signs of valvular lesions was quintupled. The authors suggest that hormone treatment is better than salicylate treatment, but admit to the difficulties encountered in making comparisons in their study with the differently treated control group.

HARVEY

Hartenstein, H., and Feldman, H. A.: Treatment of Children with Acute Streptococcal Pharyngitis with a Single Penicillin Dose. J. Pediat. 48: 318 (Mar.), 1956.

Twelve children with acute pharyngitis shown to be due to group A beta hemolytic streptococcus were treated with a single injection of a mixture of rapidly absorbed and slowly absorbed penicillin (benzathine penicillin G, 600,000 U., procaine penicillin G, 300,000 U., and buffered potassium penicillin G, 300,000 U.). The infection was cleared well by this treatment clinically within 1 to 3 days and bacteriologically within 2 days. No evidence of relapse was observed in the follow-up period of 122 days. No cases of acute rheumatic fever or nephritis developed (no type 12 streptococci were isolated). There were no reactions to the injection.

HARVEY

Brill, A. B., Ely, R. S., Done, A. K., Ainger, L. E., and Kelley, V. C.: Blood Adrenocorticotropin (ACTH) in Children with Rheumatic Fever. *J. Clin. Endocrinol.* **16:** 262 (Feb.), 1956.

Data are presented concerning the concentration of circulating ACTH in patients with various phases of untreated rheumatic fever. The subjects of the study were 32 children with rheumatic fever and 7 patients with "pure" chorea.

In patients with rheumatic fever the blood ACTH concentration was related to the phase of rheumatic activity. In children with "early acute" rheumatic fever (i.e., during the first week after onset of rheumatic symptomatology), as in normal children, there was no detectable circulating ACTH. However, in patients with "well-established" active rheumatic fever, inactive rheumatic fever, or chorea, these concentrations were elevated. Data are presented that suggest cortisone therapy depresses blood ACTH levels during the period of its administration, but that there is a return to elevated values soon after the discontinuation of cortisone. Some implications of these findings are discussed.

MAXWELL

ROENTGENOLOGY

Levy, L. M., Hannon, D. W., Sprafka, J. L., and Baronofsky, I. D.: A Method for Coronary Arteriography. *Ann. Surg.* **143:** 412 (Mar.), 1956.

A method is described for visualization of the coronary system using a single roentgen film. It involves passing a number 8 cardiac catheter down into the ascending aorta via the left carotid artery. By means of fluoroscopy the tip is located about 1 cm. above the aortic valve. Then 4 to 5 ml. of Urokon 70 per cent are injected from a syringe as quickly as possible, and by means of a switch and relay a synchronized exposure is accomplished.

With this method the authors had no fatalities in a large series of dogs.

ABRAMSON

Dalith, F.: Systolic Expansion or Aorto-Diastolic Displacement. A Roentgenkymographic Study of Left Atrial Movements in Mitral Cardiopathy. *Acta radiol.* **45:** 217 (Mar.), 1956.

The author has analyzed left atrial motion on the barium-filled esophagus in 64 patients with mitral valvular disease, registered by conventional kymography in the posteroanterior position, occasionally also in the 10 degree left anterior oblique position. He found no correlation in esophageal movements between patients with proved mitral stenosis or mitral insufficiency. He believes that esophageal displacement may occur with aortic pulsations displacing the esophagus to the right, to the left, or in both directions at once.

He concludes, therefore, that systolic expansion

is not helpful in predicting whether or not mitral insufficiency is present.

SCHWEDEL

Amundsen, P., and Sorensen, E.: Angiocardiography in Intrathoracic Tumors with Particular Reference to the Question of Operability. *Acta radiol.* **45:** 185 (Mar.), 1956.

The authors present a review of the criteria for operability in 41 patients in whom adequate rapid serial angiocardiography was performed. The authors stress electrocardiographic control during the procedure, since in 2 ventricular standstill occurred as a temporary phenomenon, which otherwise might not have been discovered. The opacifying agent must be injected rapidly, preferably by means of an automatic pressure syringe. Filling defects and displacement of the vena cava, pulmonary arteries and veins must be interpreted with caution. Blockage of the arterial or venous circulation close to the mediastinum is apt to occur in nonoperable cases.

SCHWEDEL

Idbohrn, H.: Tolerance to Contrast Media in Renal Angiography. *Acta radiol.* **45:** 141 (Mar.), 1956.

The author has surveyed the literature on renal damage following aortography for visualization of blood flow through one or both kidneys. He reports on 200 instances in which such procedures were performed, noting the effects on the nonprotein nitrogen, urinary albumin, cylindruria, and on change in kidney size before and after angiography.

Two patients developed significant azotemia, in 8 more the elevation was slight to moderate. Fourteen patients developed albuminuria, in 11 this was considerable. Seventeen developed cylindruria (RBC, casts), marked in only 1. Slight renal enlargement occurred 8 times, of considerable degree in 1. There were no deaths in this series, though in the literature a fair number have died. Multiple injections, amount and concentration of the opacifying substance, inadvertent injection directly into a renal artery seem to have been contributing factors. Endothelial arterial lesions, tubular and glomerular nephritis and lighting up of old pyelonephritis have been found in specimens excised or at autopsy following renal angiography with deleterious results.

The author indicates that renal aortography is not innocuous and suggests that renal function studies be performed prior to and after such a procedure.

SCHWEDEL

Odman, P.: Thoracic Aortography by Means of a Radiopaque Polythene Catheter Inserted Percutaneously. *Acta radiol.* **45:** 117 (Feb.), 1956.

A radiopaque polythene catheter was inserted via a Seldinger arterial needle either into the radial or femoral artery and maneuvered forward so that its tip lay in the middle part of the ascending aorta. Contrast medium solution was injected by means of a pressure apparatus.

Two sizes of catheter (internal diameters 1.25 and 0.8 mm.) were employed with distal as well as side holes to lessen pressure and recoil motion during the injection. The distal portion of the catheter may have to be curved to permit better guidance to attain the proper site where the injection is to be performed.

Thirty injections were performed, usually employing 1 ml. of 70 per cent Umbradil per Kg. body weight injected at a rate of 30 to 35 ml. per sec. The most common complication encountered was a local hematoma. In 1 instance there was local extravasation of the contrast solution requiring subsequent incision and drainage.

SCHWEDEL

SURGERY AND CARDIOVASCULAR DISEASE

Siderys, H., Grice, P. F., Shumacker, H. B., Jr., and Riberi, A.: Occlusion of the Great Cardiac Vein and Coronary Artery Ligation. *Surg., Gynec. & Obst.* **102**: 18 (Jan.), 1956. Abstracted, *Circulation* **15**: 378 (Mar.), 1957.

Warden, H. E., Read, R. C., DeWall, R. A., Aust, J. B., Cohen, M., Ziegler, N. R., Varco, R. L., and Lillehei, C. W.: Direct Vision Intracardiac Surgery by Means of a Reservoir of "Arterialized Venous" Blood. *J. Thoracic Surg.* **30**: 649 (Dec.), 1955. Abstracted, *Circulation* **15**: 257 (Feb.), 1957.

Waterman, D. H., Samson, P. C., and Bailey, C. P.: The Surgery of Patent Ductus Arteriosus. *Dis. Chest* **29**: 102 (Jan.), 1956. Abstracted, *Circulation* **15**: 230 (Feb.), 1957.

Kirklin, J. W., Ellis, F. H., Jr., and Wood, E. H.: Treatment of Anomalous Pulmonary Venous Connections in Association with Interatrial Communications. *Surgery* **39**: 389 (Mar.), 1956.

The authors reported on the surgical treatment of 6 patients with anomalous pulmonary venous connection, with or without atrial septal defects. In this condition a pulmonary vein fails to join the left atrium but instead opens into the right atrium or a systemic vein. This type of condition produces a situation in which fully oxygenated blood drains, directly or by means of some tributary, back into the right atrium and then is recirculated through the lungs. The physiologic effect is similar to that produced by an uncomplicated atrial septal defect.

In 1 of the cases the blood from the left lung drained by means of a small trunk into the left innominate vein. A small atrial septal defect existed also. The surgical attack was ligation of the anomalous pulmonary venous connection, ignoring the atrial septal defect. In another case the same situation existed, but because there was an associated large atrial septal defect, this was closed at the same time that the vessel was ligated.

In 2 other patients there was a large atrial septal defect, while the orifices of the veins of the right lung were anomalously connected with the right atrium. A proper repair of this defect was effected by suturing an Ivalon sponge in place.

ABRAMSON

Ditzler, J. W., and Eckenhoff, J. E.: A Comparison of Blood Loss and Operative Time in Certain Procedures Completed with and without Controlled Hypotension. *Ann. Surg.* **143**: 289 (Mar.), 1956.

The authors reported on a series of 90 patients in whom blood pressure had been deliberately lowered during general surgical procedures. The effect was accomplished by using Arfonad, given in the form of a continuous drip.

It was found that hypotensive anesthetic techniques reduced the amount of blood lost during major operative dissections. However, the operative time was not decreased.

The authors pointed out that deliberate hypotension may involve considerable risk to the patient. They wondered whether the advantages of the method were of sufficient degree to justify the hazard involved.

ABRAMSON

Kanar, E. A., Nyhus, L. M., Moore, H. G., Jr., Zech, R. K., and Harkins, H. N.: Experimental Vascular Grafts. IX. The Effects of Interposed Autogenous Segments on Homologous Grafts Implanted into the Thoracic Aorta of Growing Animals. *Ann. Surg.* **143**: 397 (Mar.), 1956.

The authors carried out an experimental study in an effort to obtain a vascular graft that could sustain the stress of growth satisfactorily. They found that short grafts, i.e., less than 5.0 cm., appeared to do far better than longer ones. Microscopic examination did not reveal an explanation for this difference.

The interposition of an autogenous circumferential segment between 2 segments of homologous aorta did not alter the fundamental processes that occur in homologous vascular grafts. This type of preparation failed to enlarge satisfactorily when its length was over 5.0 cm., and it was prone to develop degenerative changes following implantation into the thoracic aorta of a growing animal.

ABRAMSON

THROMBOEMBOLIC PHENOMENA

Davis, H. A., Nelson, N., Oliver, J. B., and Wallar, L. J.: A Study of Certain Factors in the Etiology of Thrombophlebitis in the Lower Extremities Following Surgery. *Am. J. Surg.* **91**: 211 (Feb.), 1956.

A statistical study was performed on 98 patients with postoperative thrombophlebitis of one or both lower extremities. In the series pulmonary embolism occurred in 24 patients, 13 females and 11 males. In the case of the males, all but one were 50 years or older. A similar relationship was not noted among the females. In 52 of the 98 patients shock or hypotension had been noted during operation.

The authors concluded that antecedent shock and hypotension occur in a statistically significant number of patients in whom thrombophlebitis develops in the lower extremities following surgery. They therefore propose these states as possible etiologic factors for the condition.

ABRAMSON

VASCULAR DISEASES

Bollet, A. J., Segal, S., and Bunim, J. J.: Treatment of Systemic Lupus Erythematosus with Prednisone and Prednisolone. *J. A. M. A.* **159**: 1501 (Dec. 17), 1955. Abstracted, *Circulation* **15**: 396 (Mar.), 1957.

Dubois, E. L., and Martel, S.: Discoid Lupus Erythematosus. An Analysis of Its Systemic Manifestations. *Ann. Int. Med.* **44**: 482 (Mar.), 1956. Abstracted, *Circulation* **15**: 365 (Mar.), 1957.

Steinberg, C. L., and Roodenburg, A. I.: Metacortandracin (Meticorten) in the Treatment of Disseminated Lupus Erythematosus and Periarthritis Nodosa. *Ann. Int. Med.* **44**: 316 (Feb.), 1956. Abstracted, *Circulation* **15**: 250 (Feb.), 1957.

Poteete, F. H., Jr., and Lynch, R. C.: Thromboangiitis Obliterans in Women: Report of Two Cases. *Surgery* **39**: 340 (Feb.), 1956.

Two cases are reported of thromboangiitis obliterans, proved histologically, in females. Both patients smoked excessively. In 1 patient lumbar sympathectomy was performed, resulting in subjective relief but little or no objective improvement. In the second patient ischemic neuritis developed 4 days after sympathectomy and pain became so severe that amputation was performed.

ABRAMSON

DeBakey, M. E.: Dissecting Aneurysm of the Aorta. *Surg., Gynec. & Obst.* **102**: 372 (Mar.), 1956.

The author proposed a new approach to the surgical treatment of dissecting aneurysm.

Prompted by the fact that in some instances survival for months or years is associated with the formation of a "double barreled" aorta, he attempted to produce such a situation surgically. He produced a re-entry passage into the aortic lumen below the pathologic origin of the dissection and obliterated the false passage beyond this point.

Such a method was employed in 10 patients, 7 of whom recovered. The results in the latter were gratifying, with complete relief of symptoms and resumption of normal activity.

ABRAMSON

Walker, A. E., and Allègre, G. E.: Carotid-Cavernous Fistulas. *Surgery* **39**: 411 (Mar.), 1956.

The authors described the clinical entity of carotid-cavernous fistulas based on a study of 24 cases. This condition is due almost always either to a head injury or to spontaneous rupture of a pre-existing aneurysm or congenital anomaly of the carotid artery into the cavernous sinus. In the case of spontaneous carotid cavernous aneurysm, an important precipitating factor is pregnancy. The condition occurs either during the latter half of pregnancy or during delivery.

The symptomatology of carotid-cavernous aneurysms consists of unilateral or bilateral exophthalmos, pulsation of the eyeball and a bruit audible to both patient and physician. In the case of the traumatic cases, the symptoms may occur immediately after the time of injury or develop a week or even months afterward.

The condition must be differentiated from orbital encephalocele, cavernous thrombosis, retro-orbital tumors, orbital vascular tumors, and aneurysms.

With regard to treatment, one approach is ligation of 1 of the carotid arteries. At the time of operation the adequacy of circulation must be tested with the carotid artery clamped before ligation is attempted.

In the present series common carotid ligation was performed in 6 cases with satisfactory results in 3. In 6 other patients the internal carotid artery was ligated and again 3 had complete relief. In 9 instances combined intracranial clipping and cervical ligation of the internal carotid artery were performed. Eight of these had complete relief initially from the operation but later all were impaired in one way or another.

ABRAMSON

Berman, J. K., Fields, D. C., Judy, H., Mori, V., and Parker, R. J.: Gradual Vascular Occlusion. *Surgery* **39**: 399 (Mar.), 1956.

The authors studied the effect of various agents in the production of slow occlusion of main vessels in animals. Of all the methods tried, they found the use of an Ameroid cylinder or ring to be the most effective. This was encased in a rigid capsule

or shell of silver or stainless steel, to withstand peripheral expansion. The material in the cylinder was a hygroscopic casein derivative that absorbed water slowly.

The Ameroid cylinder was applied to both common carotid arteries of 3 dogs, and in each instance when they were removed after 6 to 8 weeks the constriction was complete. No deleterious effects were noted in the animals.

The cylinder was also used to occlude the descending and the thoracic aorta and again complete occlusion occurred. The same type of response was noted in the case of the common hepatic artery, the inferior vena cava, the pulmonary artery, the pulmonary veins, and the coronary arteries.

It was concluded that the counterparts of clinical states could be produced experimentally by the slow occlusion of blood vessels and ducts. With such an approach remedial measures could more accurately be evaluated.

ABRAMSON

Moeller, H. C., Bernstein, L. M., Palm, L., and Grossman, M. D.: *The Effect of Protamine on Lipemia*. *J. Lab. & Clin. Med.* 47: 270 (Feb.), 1956.

Recent studies indicate that the intravenous injection of protamine causes an increase in lipid concentration in the blood. This report deals with the effect of protamine on the lipemia induced by intravenous and oral fat emulsion in human subjects and in rats.

In human subjects: (a) Simultaneous intravenous administration of protamine and fat emulsion slightly delayed the rate of removal of the fat from the blood and slightly increased the febrile response attending the infusion of the fat; and (b) intravenous infusion of protamine during alimentary lipemia produced a moderate elevation of blood lipid as compared with the control values without protamine.

In rats: (a) Protamine given intravenously increased the lipemia resulting from feeding fat; (b) when the injection of protamine immediately preceded injection of fat emulsion, removal of fat from the blood was markedly increased; but when injection of protamine preceded by 15 minutes injection of fat emulsion, marked delay in removal of fat from the blood occurred.

MAXWELL

Jones, R. J.: *Serum Cholesterol Reduction in Patients by the Oral Administration of a Brain Extract*. *J. Lab. & Clin. Med.* 47: 261 (Feb.), 1956.

Until the introduction of soya sterols, rigid restriction of dietary fat and cholesterol was the only means of reducing the level of serum cholesterol in the human. The present report deals with the effect of an orally administered cerebroside

fraction of beef brain for periods of 3 to 8 weeks in 9 subjects with coronary artery disease and hypercholesterolemia.

Mammalian brain was serially extracted with acetone and ether, and the residue was further purified by extraction with boiling ethanol. The patients took about 30 Gm. per day of the powder, which formed a gel with fluids. Control data were provided by serial determinations for 1 year, 6 months before and 6 months after the experimental period. All patients showed a reduction in mean total serum cholesterol, averaging 20 per cent for the group (range: 11 to 26 per cent). The return to control (pretreatment) values was visually not complete; there was an inconstant residual effect lasting 2 to 6 weeks after stoppage of the material. Each of the subjects also had a significant but slightly lesser reduction in phospholipid, neutral fat, and beta lipoprotein. The alpha lipoprotein was not significantly affected.

MAXWELL

Portman, O. W., Lowry, E. Y., and Bruno, D.: *Effect of Dietary Carbohydrate on Experimentally Induced Hypercholesterolemia and Hyperbetalipoproteinemia in Rats*. *Proc. Soc. Exper. Biol. & Med.* 91: 321 (Feb.), 1956.

The authors fed male albino rats diets in which the type of carbohydrate was varied and the serum cholesterol and betalipoproteins were determined over a 28-day period. Diets containing sucrose as the carbohydrate and with added cholesterol and cholic acid resulted in higher serum cholesterol and β -lipoprotein levels than in control rats in whom cornstarch was substituted for glucose. The liver cholesterol concentrations were not significantly different. Glucose and fructose produced the same effect as sucrose. Animals with cholesterol-containing diets without cholic acid and with cornstarch had somewhat lower serum cholesterol values than did animals in whom sucrose was substituted for cornstarch. Addition of sulfasuxidine produced no change in the serum cholesterol levels with sucrose-containing diets, but when cornstarch replaced sucrose in the diet, addition of sulfasuxidine resulted in elevation of serum cholesterol values to the level of that in rats fed sucrose.

MAXWELL

Bean, W. B.: *The Changing Incidence of Certain Vascular Lesions of the Skin with Aging*. *Geriatrics* 11: 97 (Mar.), 1956.

The data reported in this paper are based on a study of about 800 persons with arterial spiders and palmar erythema, 150 persons with Osler's disease, and more than 1,000 patients surveyed in detail for cherry angiomas, venous stars, and caviar lesions. Venous stars, a stellate system of collecting veins visible in the skin, increase in incidence with age, and especially in women. So do

cherry angiomas, but without the difference in sex predominance. Caviar lesions, the small, roughly spherical, or domeshaped varicose enlargements under the tongue, increase with age. The cutaneous lesion in Osler's disease (hereditary hemorrhagic telangiectasia) most often becomes a clinical problem in the third decade and so remains throughout life.

RINZLER

Spain, D. M., Greenblatt, I. J., Snapper, I., and Cohn, T.: The Degree of Coronary and Aortic Atherosclerosis in Necropsied Cases of Multiple Myeloma. *Am. J. M. Sc.* **231**: 165 (Feb.), 1956.

The degree of atherosclerosis found at necropsy in patients with multiple myeloma, cancer, and in other individuals who had died of accidental causes was compared in order to determine whether or not the lipid changes described in myeloma cases were associated with a variation in the incidence of vascular sclerosis. These changes consisted of reduced serum beta lipoprotein levels in the S_{β} 12-20 and S_{β} 20-100 classes. The degree of atherosclerosis was found to be significantly reduced in patients with multiple myeloma below that of cancer cases and "normals." The lower incidence and degree of atherosclerosis in myeloma cases is often associated with low serum cholesterol levels and rapid plasma lipid clearances.

SHUMAN

OTHER SUBJECTS

Buchman, D., and Hrowat, E. A.: Idiopathic Clubbing and Hypertrophic Osteoarthropathy. *Arch. Int. Med.* **97**: 355 (Mar.), 1956.

A case of idiopathic clubbing with early hypertrophic osteoarthropathy is presented. The patient had always considered himself in good health, and the abnormality was discovered during a routine physical examination. This report is believed to be the first that includes venous catheterization and brachial artery oxygen saturation studies, these studies being done to exclude cardiac septal defect and pulmonary disease. This case adds to those already in the literature which build a concept of simple clubbing and osteoarthropathy as manifestations of a disease of unknown cause, with a favorable prognosis.

BERNSTEIN

Young, L. J., and Cowley, R. G.: Pulmonary Infarction Complicating Mumps. *Arch. Int. Med.* **97**: 249 (Feb.), 1956.

Pulmonary infarction complicating a case of mumps in an adult is presented. This is the third such case reported according to the information available at this time. Although the source of the emboli to the lungs could not be determined, the pelvic venous plexus is postulated as the source, in view of inflammatory involvement of the lower

genitourinary tract and the complete absence of findings pointing to the veins of the legs.

BERNSTEIN

Merten, C. W., Finby, N., and Steinberg, I.: The Antemortem Diagnosis of Syphilitic Aneurysm of the Aortic Sinuses. Report of Nine Cases. *Am. J. Med.* **20**: 345 (Mar.), 1956.

Data in 9 patients with syphilitic aneurysms of the aortic sinus diagnosed during life by angiocardiology are reported and compared with those of 19 patients diagnosed at autopsy, which were reported in the literature. Two groups could be recognized: aortic sinus aneurysms associated with fusiform dilatation (aortitis) of the ascending aorta (6 patients); and localized aortic sinus aneurysms (3 patients). Unlike congenital aneurysms of the sinus of valsalva, syphilitic aneurysms may be huge and occasionally rupture outside the heart. Clinically, aortic regurgitation is an outstanding feature of aortic sinus aneurysms and was present in all but 1 patient. Heart failure, often intractable, was next in importance. Rupture of an aneurysm with creation of an aortocardiac shunt is characterized by the presence of harsh machinery-like murmurs associated with overloading of the right heart chambers and the pulmonary arterial system. Rupture of an aortic sinus aneurysm into the lesser circulation is not always immediately fatal; rupture outside the heart always causes sudden death.

The usual electrocardiographic findings of unperforated syphilitic aneurysms of the aortic sinus are left axis deviation and left ventricular hypertrophy. Roentgenologically, the presence of linear calcific deposits in the ascending aorta is good evidence of syphilitic aortitis, and was present in all but 1 patient. In several instances the conventional roentgenogram also revealed calcification in the intracardiac portion of the ascending aorta and often clearly outlined the dilated aortic sinuses. Angiocardiology demonstrates the aneurysms and their effects on the neighboring cardiovascular structures. The prognosis of syphilitic aneurysm of the aortic sinus is not necessarily ominous. During a 5-year period of observation 2 patients died; 3 were lost to observation; 4 are alive.

HARRIS

Bolt, W., and Lew, E. A.: Prognostic Value of Life Insurance Mortality Investigations. *J. A. M. A.* **160**: 736 (Mar. 3), 1956.

This article represents 15 years of experience by 27 insurance companies with more than half a million insured persons. Most of the insured people included in this investigation were white middle-class men living in urban areas. They comprised a highly select group because only the best risks in these classifications were usually granted insurance. If risks other than the best had been included, the

mortality record would undoubtedly have been higher and the record of survival poorer. Among the situations discussed here are those of apical systolic murmurs, phlebitis, epilepsy, chronic bronchitis, gastric and duodenal ulcers, gallbladder disorders, renal stone or colic, cesarean section, and a family history of cardiovascular renal disease. Despite the fact that probably some physiologic murmurs may be included, the final results show that a group of individuals with radiating systolic murmurs did show an appreciably lower survival rate. Over the 15-year period the number of deaths among those who had an apical systolic murmur without any record of rheumatic or streptococcal infection was about double that among standard risks, while the mortality among those with a record of rheumatic or streptococcal infection plus apical murmur was 2.4 times that among standard risks. Those individuals who in addition had a slight enlargement of the heart showed a 15-year survival rate of only 78 per cent, and in persons with moderate enlargement survival rate was only 66.1 per cent. This contrasts with a standard survival rate of 92 per cent. The relatively high mortality among persons with a radiating apical systolic murmur reflected excess deaths, chiefly from heart and circulatory diseases but also in this group mortality from cancer was significantly higher than normal. The reasons for this are obscure. A group of some 1,400 insured persons with a history of phlebitis was also studied. Their 15-year survival rate was 1.4 times that of the standard risks. A group of 11,600 persons who had reported 2 or more cases of cardiovascular renal disease occurring in persons under age 60 in the immediate family was studied. The risk in these individuals whose family history showed early cardiovascular renal disease was 1.4 times that among standard risks.

KITCHELL

Leslie, A., Dantes, A., and Rosove, L.: **Intermittent Positive-Pressure Breathing.** *J. A. M. A.* 160: 1125 (Mar. 31), 1956.

Thirty-three patients with pulmonary emphysema and various degrees of bronchospasm, fibrosis, bronchiectasis, and chronic infection were treated with bronchodilator drugs, with and without intermittent positive-pressure breathing. The bronchodilators used were power-nebulized and used in random sequence to determine which was most effective for each patient. The positive-pressure breathing apparatus was set for a pressure of 15 to 20 cm. water. It was noted that power nebulization of bronchodilators provided delivery of larger volumes of medicaments than is possible with hand nebulizers and is valuable in the management of bronchospastic states. This effect is not as a rule enhanced by the addition of intermittent positive-pressure breathing to the procedure. The lack of

effectiveness of therapy with intermittent positive-pressure breathing in bronchospastic states does not controvert its well-established value in resuscitation, artificial respiration, and pulmonary edema.

KITCHELL

Valles, W. C., and Riley, V.: **Rapid Procedure for Erythrocyte Packed Cell Volume and Sedimentation Rate Determinations.** *Proc. Soc. Exper. Biol. & Med.* 2: 341 (Feb.), 1956.

A modification of the conventional erythrocyte sedimentation rate and the packed-red-cell-volume procedure is described with more than a 50 per cent reduction in the operational time. The sedimentation rate and hematocrit values are determined directly in the original blood collection tube by employing a proportionate volume chart that negates the effect of sample volume fluctuations. All values are expressed as percentages rather than absolute measurements. The erythrocyte sedimentation time is reduced from 60 to 30 min. and the hematocrit centrifugation time is reduced from 30 to 10 min. These yield approximately equivalent values.

MAXWELL

Wood, E. H., Swan, H. J. C., and Helmholtz, H. F.: **The Technic and Special Instrumentation Problems Associated with Catheterization of the Left Side of the Heart.** *Proc. Staff Meet., Mayo Clin.* 31: 108 (Mar.), 1956.

The authors have designed their procedures and instrumentation to allow simultaneous measurement of aortic, left ventricular and left atrial pressure along with cardiac output. The procedure is as follows: A cardiac catheter is introduced percutaneously into an antecubital vein and an abbreviated right-heart catheterization is carried out. These measurements will usually reveal a congenital cardiac defect if one is present. The cardiac catheter is then left with its tip in the pulmonary artery for the remainder of the procedure. On completion of the right-heart catheterization, a small radiopaque arterial catheter is introduced into the descending aorta via a 19T-gage needle inserted percutaneously into a femoral artery. The rate of oxygen uptake of the patient is determined by the open-circuit method and samples of blood are withdrawn simultaneously from the pulmonary and systemic arteries for determination of cardiac output by the direct Fick method.

The patient is then rotated into the prone position, an indwelling needle is inserted into the left radial artery and left atrial puncture is carried out. The site of this puncture on the right side of the thorax is selected under fluoroscopic control exactly as described by Fisher. The interspace in the right posterior portion of the thorax selected for the puncture is the one that appears to provide the

most direct route to the center of the cardiac silhouette. The cardiac impulse can usually be felt via the needle before the tip is felt to pass through the wall of the left atrium, where a left atrial type of pressure pulse is obtained. A sample of blood is then withdrawn through a cuvette oximeter; full oxygen saturation of this sample verifies the position of the tip of the needle as the left atrium. The special adapters for introduction of a catheter through the needle and simultaneous recording of pressures via the catheter and through the needle around the catheter are then attached.

After completion of the blood pressure recordings, Evans blue dye is injected instantaneously or continuously at a constant rate into the left ventricle and the left atrium and arterial dye-dilution curves are recorded at the radial artery, left atrium, and ear. Additional curves are recorded simultaneously at the left atrium, radial artery, and ear following injection of the dye into the pulmonary artery and superior vena cava. It is the authors' belief that this procedure is practical, carries a reasonably low risk, and has much to offer in the accurate diagnosis and study of disease of the mitral and aortic valves.

SIMON

Crowley, W. P., and Parkin, T. W.: Experience with and Sequelae of Catheterization of the Left Side of the Heart Via the Percutaneous Route. *Proc. Staff Meet., Mayo Clin.* **31**: 115 (Mar.), 1956.

Catheterization of the left side of the heart via the posterior percutaneous route has been attempted in 27 patients with valvular heart disease and has been successfully completed in 26 of them. There were 12 males and 15 females in this series, the youngest patient being 14 years of age and the oldest 63 years. The preliminary clinical diagnoses of the predominant valvular lesions of the heart before left-heart catheterization were confirmed by this physiologic study in 23 of the 26 cases. It is well recognized that on occasion the clinician may find it difficult to be certain concerning the hemodynamic significance of certain lesions of the cardiac valves, and this applies particularly to the interpretation of auscultatory findings, especially when a valve is affected with both stenosis and insufficiency or when combined valvular lesions exist.

Most of these patients have been hospitalized for observation after percutaneous left-heart catheterization for 1 to 2 days. The sequelae, which have occurred following this procedure, are summarized. Pleuritic pain in the right lateral and posterior portions of the thorax was a complaint of 10 patients and persisted 1 to 4 days. Two pa-

tients expectorated small amounts of bloody sputum during the procedure, and 1 had hemoptysis the day after it. Left-heart catheterization was unsuccessful in 1 patient because a vasovagal reaction developed during the attempted insertion of the needle into the left atrium. Roentgenograms of the thorax have been obtained on the first day after left-heart catheterization in 22 of the 27 patients, and 5 of these revealed small pleural effusions or pneumonitis at the right base. Thirteen patients from this series have been operated on, and the findings of the surgeons at the time of operation confirmed the diagnosis made from the findings on catheterization with respect to the predominant valvular defect in every case. Other findings noted by the surgeon, which were thought to be related to the previous left atrial puncture, were a small amount of serosanguineous pericardial fluid in 3 patients, a small quantity of frankly bloody fluid within the pericardial sac in 3, and some fibrinous exudate over the posterior wall of the left atrium in 1.

Although the sequelae of left-heart catheterization in the authors' experience to date have been minor and of short duration, it is known that serious complications can occur. Fisher reported 1 instance of cardiac tamponade and 2 of asymptomatic hemothorax. Three deaths following left-heart catheterization have been reported in the literature. Patients should be observed carefully for at least 24 hours after this procedure and a roentgenogram of the thorax should be obtained during this period.

SIMON

Burchell, H. B., and Berkson, J.: Review of Medical Cardiac Deaths: Rochester Hospitals, 1952-53. *Proc. Staff Meet., Mayo Clin.* **31**: 75 (Feb.), 1956.

The overwhelming predominance of coronary sclerosis and hypertension as causes of cardiac deaths in the Rochester area and Clinic practice is made apparent from analysis of all medical deaths in which there was a cardiac diagnosis listed in the 2 years, 1952 and 1953. Both unusual manifestations of coronary disease, complicating features of various heart diseases, and unusual diseases per se occur with sufficient frequency to keep the diagnostician on his guard.

Administration of digitalis to the patient in the terminal illness often constituted a problem in respect to proper dosage. When the death rates per hour over the 24-hour period were studied, for the 3 daily periods (midnight to 8 a.m., 8 a.m. to 4 p.m., 4 p.m. to midnight) it was found that there was a significantly greater death rate in the evening period than in other periods.

SIMON

Millors, R. C., and Ortega, L. G.: New Observations on the Pathogenesis of Glomerulonephritis, Lipid Nephrosis, Periarteritis Nodosa, and Secondary Amyloidosis in Man. Am. J. Path. 32: 455 (May-June), 1956.

This is the third of a series of articles by the senior author and his several associates presenting evidence for the localization of gamma globulin at the site of lesions in the hypersensitivity states commonly encountered in man. The technic of labeling rabbit antibodies to human gamma globulins with a fluorescent dye and measuring by photometric means the localization of the antibody when fixed to gamma globulin in diseased human tissue is described in the preceding articles. In this article evidence is presented to show that by means of this technic gamma globulin can be shown to be present in the glomerular lesions of glomerular nephritis, in the area of necrotizing angitis in periarteritic lesions, and in the glomerular capillary walls in secondary renal amyloidosis. The authors control the experiments with well-performed studies on tissues removed routinely at autopsy from many patients with various kinds of carcinoma. They believe that this technic may become an excellent analytic tool in the further study and treatment of these hypersensitivity disease states.

HARVEY

Feigenbaum, L. Z., Watts, M. S. M., and Thomas, N. C.: Cardiovascular Case Progress Index. J. A. M. A. 161: 673 (June 23), 1956.

The natural history of chronic disease is difficult to document and the prognosis as affected by various methods of therapy is hard to measure. A cardiovascular case progress index was established in 1953 at the University of California School of Medicine as an aid to the long-range study of chronic diseases including all cases of cardiovascular disease. The index facilitates the selection of patients for teaching seminars and for research purposes as well as providing for long-term follow-up on patients.

KITCHELL

Kelly, J. J., Jr.: Salicylate Ingestion: A Frequent Cause of Gastric Hemorrhage. Am. J. M. Sc. 232: 119 (Aug.), 1956.

Three patients with recurrent gastric hemorrhage following salicylate administration were found to

have the following common features: (a) melena without ulcer symptoms, (b) bleeding without hypoprothrombinemia, (c) no roentgenographic proof of an ulcer, (d) free acid in fasting stomach contents. Gastric allergy to salicylates may have been responsible for the bleeding in cases where hemorrhage was frequent over a long period. A review of hospital records over a 4-year interval disclosed 49 cases of gastrointestinal hemorrhage of unknown etiology of which 16 were known to have received salicylate therapy for other conditions when bleeding occurred. The use of salicylates may increase the frequency of bleeding in patients with proved peptic ulcer. In addition to the possibility of allergy to salicylates as a cause of bleeding, there may be local mucosal factors and an augmentation of gastric acidity. The author suggests that the seasonal incidence of peptic ulcer activation may be explained by the more frequent use of salicylates during the "ulcer months." All patients with upper gastrointestinal hemorrhage should be questioned concerning the use of salicylates.

SHUMAN

Cole, S. L., and Corday, E.: Four-Minute Limit For Cardiac Resuscitation. J. A. M. A. 161: 1454 (Aug. 11), 1956.

Cardiac arrest is considered to have occurred when the heartbeat is no longer strong enough to be of hemodynamic significance. A total of 150 cases of cardiac arrest, 116 of them from Los Angeles alone, were collected over a 2-year period. One hundred thirty-two of these patients presented sufficient data for analysis and 33 made complete recovery. In this latter group resuscitative measures were started within 4 minutes of the diagnosis. When there was delay in the start of treatment of over 4 minutes, only 2 patients survived, and these 2 have cerebral impairment that appears to be permanent. In 36 of 45 patients who failed to respond even though treatment was within the 4-minute limit, there was evidence of cardiorespiratory embarrassment before the onset of complete arrest. It is thought that visual and auditory aids to determine the earliest sign of cardiac arrest should be used to monitor all patients undergoing operation. To increase the percentage of recovery in cardiac arrests, more physicians must be trained to take precise action within the 4-minute limit.

KITCHELL

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, NEW YORK 10, N. Y.

Telephone Gramercy 7-9170

AHA ANNOUNCES AWARDS TO 155 INVESTIGATORS

A total of 155 research investigatorships and fellowships have been announced by the Association for the fiscal period beginning July 1, 1957 through June 30, 1958. The awards represent an expenditure of \$977,000. The national research program, which the Heart Association supports jointly with its state and local affiliates, is financed through public contributions to the annual Heart Fund appeal.

Included are three career investigatorships, 80 established investigatorships, and 72 research fellowships. The \$977,000 awarded in these categories represents an increase from \$825,000 in the same categories last year. Still to be awarded are grants-in-aid for research projects which will be announced later this year.

The new awards raise to approximately \$19,000,000 the sums allocated for cardiovascular research by the American Heart Association and its affiliates since 1948. In addition to the affiliates' share in the national research program, local Heart Associations support research studies in their own areas. A complete list of award recipients appears at the end of this section.

ABSTRACTS OF AHA SCIENTIFIC SESSIONS PAPERS DUE JUNE 15

CONFERENCE PROCEEDINGS TO BE PUBLISHED

The proceedings of the Council for High Blood Pressure Research, which met in Cleveland November 30-December 1 last year, will be published by the American Heart Association on or before June.

The transactions of the Conference on Cerebral Vascular Diseases held in Princeton in January will be published under the auspices of the American Heart Association by Grune and Stratton, Inc., 381 Fourth Ave., New York City.

MICHIGAN CONFERENCE ON HYPERTENSION

A University of Michigan Regional Conference on Hypertension will take place in Ann Arbor, Michigan, June 7-8, 1957 in recognition of the twenty-fifth anniversary of the first production of experimental renal hypertension by Dr. Harry Goldblatt. Reports will be presented on the basic mechanisms of renal hypertension, including adrenal, neurogenic and renoprival aspects.

Those desiring to attend are urged to write well in advance for information and reservations to Dr. John Sheldon, Director, Department of Post Graduate Medicine, University of Michigan Medical School, University Hospital, Ann Arbor, Mich.

1956 AHA ANNUAL REPORT ISSUED

The American Heart Association's 1956 annual report, entitled "Lifelines of the Heart," describes the continued, "almost headlong" growth of heart surgery as last year's outstanding achievement in cardiovascular medicine.

The "lifelines" are described as the circuit of research, lay and professional education, and community services, which constitute the program of the American Heart Association. Calling research the "source of the lifeline," the report notes that in 1956 the American Heart Association spent 55 cents out of every dollar received by its national office to underwrite scientific studies in the cardiovascular field. The total thus expended in 1956, by both the national organization and its affiliates, was close to \$5,000,000, or approximately \$1,100,000 more than in 1955.

MEETINGS CALENDAR

April 15-19: Federation of Medical and Biological Societies, Chicago. Cyrus C. Erickson, 858 Madison Ave., Memphis 3, Tenn.

April 22-27: American Academy of Neurology, Boston. T. W. Framer, University of North Carolina, Chapel Hill, N. C.

- April 26-May 2: Society for American Bacteriologists, Detroit. J. W. Bailey, Sterling-Winthrop, Research Institute, Rensselaer, N. Y.
- May 5: American Federation for Clinical Research, Atlantic City, N. J. William W. Stead, Veterans Hospital, Minneapolis 17, Minn.
- May 5-10: National Tuberculosis Association, Kansas City, Mo. Mrs. Morrell DeReign, 1790 Broadway, New York 19, N. Y.
- May 6-9: American Urological Association, Pittsburgh. Samuel L. Raines, 188 S. Bellevue Blvd., Memphis, Tenn.
- May 7-8: Association of American Physicians, Atlantic City, N. J. P. B. Beeson, Yale University School of Medicine, New Haven, Conn.
- May 8-10: American Surgical Association, Chicago. E. Kennedy Gilchrist, 59 E. Madison St., Chicago, Ill.
- May 13: Scientific Meeting of the New England Cardiovascular Society, Boston. Alexander S. Nadas, M.D., Secretary, The New England Cardiovascular Society, % The Massachusetts Heart Association, 650 Beacon St., Boston 15, Mass.
- May 15-18: First Wisconsin Conference on Work and the Heart, Milwaukee. Elston L. Belknap, M.D., Marquette University School of Medicine, 561 N. 15th St., Milwaukee 3, Wis. By invitation.
- May 27-29: American Gynecological Society, Hot Springs, Va. A. A. Marchetti, 3800 Reservoir Rd., N. W., Washington 7, D. C.
- May 29-June 2: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago, Ill.
- May 30-31: American Geriatrics Society, New York. Richard J. Kraemer, Greenwood, R. I.
- June 1: American Academy of Tuberculosis Physicians, New York. Oscar S. Levin, P. O. Box 7011, Denver 6, Colo.
- June 2: American Society for Vascular Surgery, New York. Henry Swan, 4200 East 9th Ave., Denver 20, Colo.
- June 3-7: American Medical Association Annual Meeting, New York. George F. Lull, M.D., American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.
- June 7-8: University of Michigan Regional Conference on Hypertension, Ann Arbor, Michigan. John Sheldon, M.D., Department of Post Graduate Medicine, University of Michigan Medical School, University Hospital, Ann Arbor, Mich.
- June 16-21: American Society for Pediatric Research, Carmel, Calif. Sydney S. Gellis, 330 Brookline Ave., Boston 15, Mass.
- June 17-19: American Pediatric Society, Carmel, Calif. A. C. McGuinness, 1427 Eye Street, N.W., Washington 5, D. C.

ABROAD

- April 10-11: Third Congress of the Israel Heart Society, Jerusalem. Dr. Karl Braun, Hadassah University Hospital, Jerusalem, P.O.B. 499.
- June 3-7: Harvey Tercentenary Congress, London. D. Geraint James, M.D., M.R.C.P. 11 Chandos Street, Cavendish Square, London W.1.
- June 23-28: International Congress on Rheumatic Diseases, Toronto, Ont. International Congress on Rheumatic Diseases, P. O. Box 237, Terminal "A", Toronto, Ontario, Canada.
- July 7-13: Brazilian Congress of Cardiology and Angiology, Rio de Janeiro. Dr. A. de Carvalho Azevedo, Rua Domingos Ferreira 28, Rio de Janeiro, Brazil.
- July 14-19: International Gerontological Congress, Merano-Bolzano, Italy. Segreteria, Quarto Congresso Internazionale de Gerontologia, Viale Morgagni 85, Firenze, Italy.
- July 21-28: International Congress of Neurological Sciences, Brussels, Belgium. Pearce Bailey, M.D., National Institute of Health, Bethesda 14, Md.
- July 24-29: International Congress of Nutrition, Paris. Congress International de Nutrition, 71 Blvd. Pereire, Paris 17^e, France.
- September 14-21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

AHA AWARD RECIPIENTS

Following is a list of career investigators, established investigators and research fellows selected for support during the fiscal year beginning July 1, 1957 by the Association's Research Committee.

Career Investigators

- Lorber, Victor*, University of Minnesota Medical School, Minneapolis.
- Pappenheimer, John R.*, Harvard University Medical School, Boston.
- Coons, Albert H.*, Harvard University Medical School, Boston.

Continued Established Investigators

- Abelmann, Walter H.*, The circulation in disorders of metabolism and the regulatory role of the circulation. Harvard Medical School, Boston.
- Aikawa, Jerry Kazuo*, Immunophysiology, University of Colorado School of Medicine, Denver.
- Barker, Earl Stephens*, Studies in renal physiology, normal and pathologic; University of Pennsylvania Hospital, Philadelphia.
- Beck, William Samson*, The mechanism by which hydrogen made available by carbohydrate oxidation is utilized for fatty acid synthesis; New York University College of Medicine, New York.

- Benesch, Reinhold*, The role of sulfhydryl and disulfide groups in biological systems; Marine Biological Laboratory, Woods Hole, Mass.
- Boyle, Edwin, Jr.*, Comparative studies in lipoprotein transport and metabolism concerning atherosclerosis in man, monkey and pigs; Medical College of South Carolina, Charleston.
- Briller, Stanley Arthur*, Energetics of the myocardium; New York University College of Medicine, New York.
- Brodsky, William Aaron*, Renal and electrolyte metabolism; University of Louisville School of Medicine, Louisville, Kentucky.
- Cohn, Mildred*, Mechanisms of phosphorylation and phosphate transfer reactions; Washington University School of Medicine, St. Louis, Missouri.
- Conn, Hadley L., Jr.*, The alterations in pressure-volume-flow relationships produced by direct cardiovascular stresses, and the effect of these alterations on transcapillary kinetics and organ metabolism; University of Pennsylvania Medical School, Philadelphia.
- Curran, George Lally*, The metabolic aspects of cardiovascular disease with particular reference to lipid metabolism; University of Kansas Medical Center, Kansas City.
- Drell, William*, Biochemical studies of the sympathetic nervous system in relation to cardiovascular function; University of California School of Medicine, Los Angeles.
- DuBois, Arthur Brooks*, Gas exchange in the lungs, mechanics of breathing and pulmonary capillary blood flow; University of Pennsylvania, Philadelphia.
- Eckstein, Richard W.*, The coronary collateral circulation, the oxygen consumption of the right ventricle; Western Reserve University School of Medicine, Cleveland.
- Elkinton, J. Russell*, Interrelationships of cardiovascular functions and electrolyte physiology; University of Pennsylvania School of Medicine, Philadelphia.
- Epstein, Franklin H.*, Metabolic and circulatory factors affecting the distribution and excretion of water and electrolytes; Yale University School of Medicine, New Haven.
- Farber, Saul J.*, The role of electrolytes and their relationship to extracellular and intracellular organic constituents in heart disease. New York University College of Medicine, New York.
- Flavin, Martin, Jr.*, Enzyme chemistry and intermediary metabolism; New York University College of Medicine, New York.
- Foulkes, Ernest Charles*, Fundamental mechanisms of electrolyte transport across biological membranes; The May Institute for Medical Research, Cincinnati.
- Gaudino, Mario*, The intracellular and extracellular distribution of water and electrolytes in the organism; New York University College of Medicine, New York.
- Gergely, John*, Biochemical and biophysical studies on cardiac and skeletal muscle contraction; Massachusetts General Hospital, Boston.
- Goldthwait, David Atwater*, The biosynthesis of purine nucleotides; Western Reserve University School of Medicine, Cleveland.
- Goodall, McChesney, Jr.*, Effect of cervico-stellate ganglionectomy on the adrenaline and noradrenaline content of sheep heart; unknown sympathetic factor present in mammalian heart; Duke University Medical School, Durham, N. C.
- Goodyer, Allan V. N.*, Hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes; Yale University School of Medicine, New Haven.
- Grisolia, Santiago*, Enzymatic patterns of nitrogen metabolism in heart muscle; University of Kansas Medical School, Kansas City.
- Gross, Jerome*, Studies on the structure, composition, genesis, function and malfunction of connective tissues; Massachusetts General Hospital, Boston.
- Havel, Richard J.*, Mechanisms of lipid transport and the relation of altered lipid transport to atherogenesis; University of California School of Medicine, San Francisco.
- Kaplan, Melvin*, Attempt to localize tissue-deposited streptococcal antigens and antibodies in animal and human tissues by means of the fluorescein-labeling technique. Children's Medical Center, Boston.
- Kun, Ernest*, Pathway of the metabolism of hydroxy acids; University of California School of Medicine, San Francisco.
- Kuo, Peter T.*, Intravascular distribution of lipid particles in clinical arteriosclerosis. Hospital and School of Medicine, University of Pennsylvania, Philadelphia.
- Lazzarini, Abel Alfred, Jr.*, Metabolic and immunological changes occurring in transplanted tissues; New York University Post-Graduate Medical School, New York.
- Lepeschkin, Eugene*, Basic problems of electrocardiography; University of Vermont College of Medicine, Burlington, Vermont.
- Linker, Alfred*, Studies on mucopolysaccharides; Columbia University, New York.
- Mackler, Bruce*, Metabolic sequences involved in electron transport in mammalian tissues; University of Wisconsin, Madison.
- Mateer, Frank M.*, (1) Cardiovascular effects of specific electrolyte depletion and repletion studied by means of dialysis technique; (2) Ballistocardiographic studies in the normal and abnormal subject; University of Pittsburgh School of Medicine, Pittsburgh.

- Mathews, Martin B.*, The physical chemistry of the acid mucopolysaccharides of connective tissue and their protein complexes; University of Chicago, Chicago.
- Micalfe, James*, Changes in the maternal circulation during pregnancy and labor; Boston Lying-in Hospital, Boston.
- Mommaerts, Wilfried F. H. M.*, Chemical-physiological studies on contractile tissues; University of California Medical Center, Los Angeles.
- Nelson, Clifford Vincent*, (a) The mechanism of fibrillation; (b) Quantification of the vectorcardiogram; Maine Medical Center, Portland.
- Osborn, John J.*, Extra-corporeal circulation, physiology of hypothermia, and intracellular fluid and ionic shifts during respiratory acidosis; Stanford University School of Medicine, San Francisco.
- Peterson, Philip Young*, '48; Pathogenesis of selected forms of tissue damage; University of Virginia School of Medicine, Charlottesville.
- Perry, Horace Mitchell, Jr.*, Pathogenesis and treatment of hypertension and atherosclerosis; Washington University School of Medicine, St. Louis, Missouri.
- Plaut, Gerhard W. E.*, Pathways and compounds of intermediary metabolism with particular regard to the properties of heart muscle; New York University College of Medicine, New York.
- Rose, John C.*, Studies of the circulation in the dog using a mechanical left ventricle. Studies in aortic insufficiency; on the relationship between arterial pressure and cardiac auscultatory phenomena; Georgetown University Medical Center, Washington, D. C.
- Sanadi, D. Rao*, Studies on (a) Oxidative phosphorylation and (b) Amino acid metabolism; University of California Medical School, Berkeley.
- Schmidt-Nielsen, Bodil M.*, Comparative kidney physiology; Duke University School of Medicine, Durham, North Carolina.
- Schwartz, William B.*, Disorders of electrolyte metabolism and kidney function; New England Center Hospital, Boston.
- Schweel, Richard*, The biological synthesis of protein; California Institute of Technology, Pasadena, California.
- Singer, Thomas P.*, Oxidative metabolism of sulfur amino acids in animals; metabolism and function of new coenzymes; Henry Ford Hospital, Detroit.
- Slade, Hutton Davison*, The biochemistry of the group "A" hemolytic streptococcus; The Rheumatic Fever Research Institute, Chicago.
- Spencer, Merrill P.*, Factors affecting distribution of cardiac output; Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.
- Srinson, David B.*, (a) Biochemistry of one-carbon intermediates; (b) Biosynthesis of aromatic compounds in bacteria; Columbia University College, New York.
- Samler, Jeremiah*, Experimental atherosclerosis; Experimental hypertension, renal function in edema formation; Michael Reese Hospital, Chicago.
- Stavitsky, Abram B.*, Studies on the basic mechanisms of anti-body production in vivo and in vitro; Western Reserve University School of Medicine, Cleveland.
- Stefanini, Mario*, Establishment of "profile" of tests for diagnosis of thrombotic tendency; relation of the endocrine system to the blood coagulation mechanism and the pathogenesis of thromboembolism; possibilities of employment of fibrinolysin in the treatment of thromboembolism; St. Elizabeth's Hospital, Brighton, Mass.
- Stetson, Chandler A.*, Investigations in rheumatic fever; New York University, New York.
- Szent-Gyorgyi, Andrew Gabriel*, The structure of myosin; Institute for Muscle Research, Woods Hole, Massachusetts.
- Thal, Alan Philip*, (1) Revascularization of the myocardium; (2) The mechanism of action of bacteria and bacterial toxins on small blood vessels; University of Minnesota Medical School, Minneapolis.
- Wessler, Stanford*, The pathogenesis of intravascular thrombosis; Beth Israel Hospital, Boston.
- Zweifach, Benjamin William*, Biochemical analysis of structural elements of blood-tissue barrier; New York University, New York.

Continued Research Fellows

- Campbell, Edmund West*, The mechanism of platelets, platelet constituents and allied factors in blood coagulation and thrombosis; New England Center Hospital, Boston.
- Khairallah, Philip Amin*, Mechanisms of action of vaso-active agents on muscle and nerve tissue, Cleveland Clinic, Cleveland.
- Maley, Gladys Feldott*, Oxidative phosphorylation, New York University College of Medicine, New York.
- Ullick, Stanley*, The relation of aldosterone to edema; Columbia University, New York.
- Wellaufer, Donald Burton*, (I) The interactions of calcium and magnesium with myosin; (II) Hydrogen bonds in the stabilization of protein configurations; Harvard University, Cambridge.

Renewal Research Fellows

- Attinger, Ernst O.*, Correlation of dynamics of pulmonary ventilation and circulation; Boston City Hospital, Boston.
- Adolph, Robert J.*, Effect of digitalis on heart and muscle electrolytes; University of Illinois, Chicago.
- Birkhead, Newton Charles*, (1) Thoracic aorta blood flow in mitral valve disease; (2) The evaluation of indigo carmine as an indicator for arterial dilution curves; Mayo Foundation, Rochester, Minnesota.

- Boucot, Nancy G.*, Carbohydrate metabolism in uremia; Peter Bent Brigham Hospital, Boston.
- Brady, Allan J.*, Efflux of sodium and potassium from frog ventricle; Cambridge University, Cambridge, England.
- Connor, William Elliott*, Lipid metabolism in atherosclerosis; State University of Iowa, Iowa City.
- Corcoran, John W.*, Biosynthesis of vitamin B-12; Columbia University, New York.
- DeWall, Richard Allison*, Perfusion techniques as an aid to open intracardiac surgery; University of Minnesota, Minneapolis.
- Dickerman, Herbert William*, (1) Isolation, purification and characterization of nicotinamide ribotidase; (2) Synthesis of pyridine nucleotides in embryonic heart tissue; The Johns Hopkins University, Baltimore.
- Feinberg, Harold*, Determinants of coronary flow and cardiac metabolism; Michael Reese Hospital, Chicago.
- Gonzalez, I. Ernest*, (1) The influence of steroids on canine and human liver lipids, serum lipids and lipoproteins; (2) The influence of steroid hormones on the histochemistry of the vascular bed and its response to injury: A study in atherogenesis; Oklahoma Medical Research Foundation, Oklahoma City.
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Congenital Cardiac Defects: A Physician's Guide for Evaluation and Management

Report of the Committee on Congenital Heart Disease

RUTH WHITTEMORE, M.D., *Chairman*

This report was designed primarily for the physician who is not a cardiologist but who encounters, in the course of his practice, patients with congenital malformations of the heart. It will help him decide whether and when such patients should have special studies done in a cardiac center or by a cardiologist familiar with these problems. It is divided into three parts: one on infants, one on children and adults, and the last on management. The first two parts are designed to assist the physician in the selection of patients for special studies, the last to aid him in the management of patients under his care. A special section in part III is devoted to care of the pregnant woman with a congenital defect. The decision as to which studies are needed and when they should be performed should be left to the cardiologist or center to which the patient is referred.

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PART I—SIGNS AND SYMPTOMS IN INFANTS

General Considerations

EVEN though a malformation of the heart is present at birth, such a condition does not necessarily remain static. Many malformations increase the work of the heart, and some cause a *progressive increase* which results in progressive cardiac enlargement, cardiac failure, and even death.

Congenital malformations of the heart are a major cause of death during infancy. Cardiac surgery can be—and has been—performed successfully on infants, even in the first weeks of life. However, the mortality rate at this early age is high. It is better to defer surgery, if possible, until childhood; but *the risk of waiting must be weighed against the operative mortality*. The decision to operate or not is a difficult one and calls for cardiac evaluation early in life by specially trained physicians.

An infant with a congenital defect requires more frequent observations during the first two years of life than he does in later childhood.

This is a report of the Committee on Congenital Heart Disease of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association and reflects that committee's findings in the matter under study.

Growth is very rapid during this period: by the time an infant is two months old he has doubled his age of a month before, and normally by the time he is four or five months old he has doubled his birth weight.

For this reason, a baby with a heart murmur should be examined at monthly intervals and special attention should be paid to weight gain, heart size, changing murmurs and development of cyanosis.

In general, *an infant with a heart of normal size, whose activity is normal, who has normal color, and who gains weight normally*—even though a cardiac defect is diagnosed—does not need special studies such as cardiac catheterization or angiocardiology. Nevertheless, since his condition may change, he should be kept under observation.

Indications for Prompt Evaluation

Any of the following manifestations indicates that further study should be done promptly.

Listed in order of frequency, they are:

- Dyspnea in a previously asymptomatic infant
- Increasing size of the heart
- Changing murmurs
- Easy fatigability

Failure to gain weight
Increasing cyanosis
Increasing polycythemia

Indications for Immediate Evaluation

Any of the following manifestations calls for immediate diagnosis and treatment:

Attacks of paroxysmal dyspnea which progress to syncope
Progressive cyanosis with dyspnea (even in the absence of a murmur or of cardiac enlargement)
Stridor or choking spells
A ventricular rate of over 200 per minute, lasting for several hours
Cerebral vascular accidents—manifested by:
 hemiplegia
 convulsions
 other neurologic signs
Marked cardiac enlargement
Cardiac failure

Signs of Cardiac Failure in Infants

Cardiac failure in infants is manifested by:
Rapid respirations
Enlargement of the heart
Gallop rhythm
Engorgement of the liver
Rales in the lungs—usually a late manifestation
Pitting edema—a very late and often an ominous manifestation

Important Clues

The first sign to suggest a cardiac malformation is usually a murmur. It is not, however, a reliable sign. A murmur in the newborn may disappear and not represent a congenital defect. On the other hand, a murmur resulting from a malformation may not be heard until later in infancy.

Color. A cardiac defect is the most common cause of persistent cyanosis. Cyanosis may appear at or shortly after birth, or perhaps not be visible for several months or even years. Persistent cyanosis usually leads to polycythemia, although this may be absent in early infancy. Rapidly increasing polycythemia is

always cause for concern. For an estimate of the severity of polycythemia, the hemoglobin and hematocrit determinations are quite as important as the red blood cell count. A hemoglobin content over 20 Gm., a hematocrit reading over 70 per cent, or a red blood cell count of 7,500,000 per mm.³ is clear indication for immediate evaluation.

Pallor in an infant suggests *anemia*. Anemia is known to increase the work of the heart and may therefore require treatment.

Weight. Normal weight gain usually indicates satisfactory progress. The outstanding exception is the infant with valvular pulmonary stenosis and intact ventricular septum, in whom a normal weight gain is the rule.

Failure to gain nearly always points to serious cardiac trouble. In the cyanotic infant it is of ominous significance.

Increase of weight due to edema is a late indication of serious cardiac failure.

Fatigue. One of the earliest manifestations of fatigue in infancy is an excessive length of time required to take even small feedings. Shortness of breath causes the multiple interruptions in the feeding. Labored breathing may also accompany such acts as defecation.

Later, an early manifestation of fatigue may be a shorter duration of effort, as in creeping or walking, in comparison with other young children of similar age.

Respiration. Changes in the rate or character of the respirations are often the earliest manifestations of distress.

The development of tachypnea in an infant with a murmur suggests the onset of early heart failure.

Attacks of *paroxysmal dyspnea* are common in infants with cyanotic malformations, particularly infants in whom there is decreased pulmonary flow. In most cases, such attacks do not represent cardiac failure. Episodes of paroxysmal dyspnea are characterized by sudden onset of labored breathing and increasing cyanosis, often with an expiratory grunt. Attacks may be precipitated by exertion, excitement, febrile illness; or they may occur without any apparent cause. They do not usually last long but may be prolonged or

severe and end in syncope. Such attacks are occasionally fatal.

Attacks of *stridor* may be due to a vascular ring which compresses the trachea and the esophagus. Such stridor is often accompanied by a brassy cough or choking spells.

Pulse. Although the heart rate of a normal infant is considerably higher than that of a child or adult, a rate of 200 or more is always of concern. Even in an infant with a normal heart, *paroxysmal tachycardia* may result in cardiac failure. Any attack which persists 4 to 6 hours requires specific treatment.

A readily palpable radial pulse combined with a weak or absent femoral pulse usually indicates coarctation of the aorta. For this reason, palpation of femoral pulses should be part of any routine examination.

Heart Size. The size of the heart in an infant is difficult to determine by physical examination alone. Progressive increase in the heart size out of proportion to the growth of the chest is serious; on the other hand, a relative decrease of cardiac size is a good sign. X-ray and fluoroscopic examinations allow an accurate determination of the size and configuration of the heart and of the vascularity of the lung fields. It is usually possible to determine whether the pulmonary blood flow is approximately normal, increased, or decreased. (In infants, the shadow of the *thymus* superimposed on the shadow of the heart may give a false impression of cardiac enlargement.)

Caution. The physician must remember the dangers of excessive exposure to roentgen rays and therefore control the length and number of fluoroscopic and x-ray examinations.

Electrocardiogram. The electrocardiogram is seldom useful in the selection of patients to be sent to a cardiac center. It is valuable, however, in the differential diagnosis of cardiac malformations and in the clarification of arrhythmias. It is often helpful, too, in the detection of digitalis intoxication. Serial electrocardiograms may aid in the demonstration of progressive changes.

The age of the infant should always be taken into consideration. The rate, conduction intervals, axis deviation and form of the complexes

vary with age. There are many electrocardiographic patterns in infants within the variations of normal.

PART II—SIGNS AND SYMPTOMS IN CHILDREN AND ADULTS

General Considerations

All children and adults suspected of heart disease should be given the benefit of detailed cardiac study. Early evaluation enables the cardiologist to assess subsequent changes.

Every *child* with a malformation of the heart should have a yearly cardiac examination by his physician. This should include an x-ray of the chest. The patient should be seen by a physician experienced in pediatric cardiology at regular intervals during childhood and more frequently during puberty. How frequent these check-ups should be depends on the type of malformation.

Change in murmurs, development of new symptoms, or increase in the size of the heart are always indications for prompt re-evaluation. A physician experienced in pediatric cardiology is in the best position to determine the proper time for special studies and, together with the cardiac team, to determine which procedures, if any, will provide the most needed information.

Adolescent patients must be followed closely. The spurt of growth and the increase in strenuous physical activity common at this age may increase the strain on the heart.

Every *woman* with a cardiac defect should be carefully evaluated before she marries. If she has not had a cardiac evaluation prior to pregnancy, it should be done at the earliest possible date.

Indications for Prompt Evaluation

Any one of the following signs indicates that cardiac evaluation should be done promptly.

Listed in order of frequency, they are:

- Shortness of breath
- Decreased exercise tolerance
- Cyanosis
- Abnormalities of heart rate or rhythm
- Cardiac enlargement
- Changing cardiac murmurs

Cardiac failure

Hypertension

Retardation of growth or development

Progression of any signs or symptoms calls for prompt re-evaluation.

Common Cardiac Defects Amenable to Surgery

Surgery may be advisable—and possible—for many children and adults with congenital defects. The following paragraphs list some of the signs associated with defects that are operable during childhood:

A continuous murmur over the pulmonary area in a noncyanotic child usually indicates *patent ductus arteriosus*. An operation to correct this defect is best done before the child enters school.

A strong pulse in the upper extremities, combined with a weak or absent pulse in the lower extremities, suggests *coarctation of the aorta*. It is advisable to defer surgery until between the eighth to twelfth year if the child's heart is of normal size and his blood pressure is not excessively elevated.

Cyanotic children who squat when they are tired usually have pulmonary stenosis and decreased pulmonary blood flow as in *tetralogy of Fallot*. These children can frequently be helped by surgery.

Patients with a harsh systolic murmur over the pulmonary area and a weak or absent pulmonic second sound may have valvular *pulmonary stenosis with an intact ventricular septum*. Surgery is usually indicated if these patients show dyspnea, cyanosis, cardiac enlargement, or electrocardiographic evidence of marked right ventricular hypertrophy.

Closure of certain septal defects are being considered in a few cardiac centers.

Important Clues

Color. Pallor is an important sign and may be due to anemia. Severe anemia, regardless of etiology, may of itself cause murmurs or cardiac enlargement.

Persistent cyanosis of the mucous membranes usually indicates a venous-arterial shunt. Cyanosis may occur at any age and may appear

initially only on exertion or increase with stress. Usually it leads to polycythemia.

Relative anemia may occur in a cyanotic child, and the greater the anemia the less obvious is the cyanosis. It must be remembered that in every instance as much as 5 Gm. per cent of reduced hemoglobin circulates in the blood before cyanosis becomes visible. For instance, in the presence of a total hemoglobin of 14 Gm., the cyanotic child has less than 9 Gm. per cent of oxyhemoglobin. Therefore, in the presence of cyanosis, any anemia indicates a greater deprivation of oxygen than is indicated by the hemoglobin level.

Clubbing occurs in most patients with cardiac malformation associated with long-standing cyanosis. It may, however, occur as a manifestation of chronic pulmonary disease and bacterial endocarditis, and occasionally it appears in normal individuals as a familial trait.

Growth and Development. Although many children with cardiac defects grow normally in height and weight, children who have large shunts often grow more slowly than normal children and may develop a "gracile habitus." Retarded growth may be the first indication that cardiac output is inadequate to meet the demands of the body, as in large left-to-right shunts or severe anoxia.

A sudden gain in weight may indicate edema due to congestive failure.

Exercise Tolerance. A large majority of patients with congenital malformations are able to lead normal, active lives without undue fatigue or strain. Reduced exercise tolerance is an indication for referral. Minor changes of exercise tolerance in the cardiac child are difficult to evaluate because of considerable variations in the activities of normal young children. Comparison of the child's play activities with those of playmates or siblings is often helpful. The cardiac child, for example, may seek quieter games, rest more frequently, or stop active play sooner than do other children of his age.

Cyanotic patients limit their own activity. Some cyanotic children are unable to walk more than a few feet without having to rest. They

often assume a squatting position or insist on being carried. As they grow older their exercise tolerance usually improves. If it does not, re-evaluation is indicated.

Respiration. *Dyspnea on exertion*, a frequent complaint, is variable and requires evaluation. It may easily be overlooked in patients with large left-to-right shunts. In a cyanotic child extreme dyspnea often precedes the need for immediate rest and in most instances is quickly relieved by the squatting position. In the young cyanotic child such respiratory distress may progress to an attack of *paroxysmal dyspnea*, with or without loss of consciousness. In the older child these attacks are less frequent, but if they occur they are a sign of severe anoxia.

Pulse and Blood Pressure. In any patient, child or adult, the physician should palpate the pulses of the upper and lower extremities and record the blood pressures. He should note any discrepancy between the blood pressures in the two arms or between the arms and legs and should watch for *hypertension in the upper extremities*. In some instances, abnormal pulsations may be seen in the neck or collateral pulsations felt over the thoracic cage.

An abnormal pulse pressure is also significant in many congenital malformations.

The pulse may reveal certain *abnormal cardiac rates or rhythms*, such as atrial fibrillation, paroxysmal tachycardia, ectopic beats and complete atrioventricular dissociation. The latter should be suspected in a child with a pulse lower than 60. It is wise to confirm the nature of these abnormalities by an electrocardiogram.

Heart Sounds and Murmurs. The quality of heart sounds is always important: a forceful heart sound may indicate a laboring heart; poor quality of heart sounds or gallop rhythm may indicate impaired myocardial function; a widely split pulmonic second sound, or its absence, diminution, or increase in intensity, is usually abnormal.

A question of great practical importance is whether a murmur is innocent or organic in origin.

Innocent (nonsignificant or "functional")

murmurs are extremely common, occurring at one time or another in over 50 per cent of children. Such murmurs are systolic and are usually located along the left or upper right sternal border. They are vibratory or groaning, poorly localized, and may vary on change of position.

A *venous hum* is also innocent; it is a high-pitched continuous bruit heard lateral to the base of the heart, above or below either clavicle. This hum usually disappears when the patient lies down or when pressure is applied over the jugular vessels. It varies greatly on turning the patient's neck.

Systolic murmurs associated with a thrill are usually organic. Their quality, intensity, and location are important in the differentiation of congenital defects from acquired heart disease.

A harsh systolic murmur and thrill close to the sternum or over the base of the heart are more often indicative of congenital than acquired heart disease.

Diastolic murmurs other than those associated with a venous hum are organic. It is important to differentiate between a short diastolic murmur and a third heart sound.

Apical or basal diastolic murmurs, particularly with cardiac enlargement, occur not only in certain congenital malformations of the heart but also in acute rheumatic fever and rheumatic heart disease. (An analysis of the murmurs of rheumatic fever and rheumatic heart disease will be found in "Jones Criteria (Modified) for the Diagnosis of Rheumatic Fever."¹)

In most cases, a *continuous murmur* over the pulmonic area is due to a patent ductus arteriosus. It is usually audible in childhood but occasionally does not develop until the child is about 5 years old. This murmur is usually accentuated by exercise and is often better heard in the recumbent than in the erect position. This must be differentiated from the venous hum. Continuous murmurs may also be noted in cyanotic patients or in those with less common cardiac defects.

Cardiac Size and Configuration. The cardiac configuration, enlargement of specific chambers, and pulmonary vascularity are easier to

evaluate with x-ray in children and adults than in infants. Serial x-rays are important aids in the detection of a progressive increase in heart size or changes in vascular markings.

X-rays for size of the heart should be standard teleroentgenograms taken six feet (or 2 meters) from the roentgen tube.

Fluoroscopy aids in the study of:

- Size and configuration of the heart and its chambers
- Pulsations of the cardiac border
- Vascularity of the hilar shadows
- Course of the barium-filled esophagus
- Position of the aorta and anomalous vascular structures.

Fluoroscopy should be a part of the roentgenographic study of the heart and preferably be performed by the cardiologist.

Caution. The amount of total x-ray exposure to the patient should always be carefully limited.

Electrocardiogram. An electrocardiogram is an important adjunct in the cardiac evaluation and should always include precordial leads. Cardiac arrhythmias should be confirmed by electrocardiogram.

The age of the child always should be taken into consideration in the interpretation of the electrocardiogram as the range of normal measurements varies according to age and pulse rate of the individual child and differs from the norms established for adults.

PART III—MANAGEMENT

Attitude and General Care

The physician should encourage parents to allow the cardiac child to lead as normal a life as possible. He should remind them not to spoil the child. Both physician and parent should maintain a cheerful outlook; this is certainly justifiable, as a malformation which cannot be helped at the present time may well become amenable to surgery in the near future.

The child with a cardiac defect should be given immunizations, particularly pertussis vaccine, at the usual time. Education is just as important as for normal children and whenever possible the cardiac child should attend a regular school.

Physical Activity

An infant need not be restricted in any way; he should be allowed to crawl and walk as he likes. It is not harmful to let him cry. In general, it is both unwise and unnecessary to restrict the young child with a congenital defect so long as he can rest easily and without embarrassment when he chooses. For the older child, the physician can outline a suitable program of physical activities after the child's cardiac status and functional capacity have been evaluated.

Protection Against Bacterial Endocarditis²

In individuals who have congenital heart disease, as in those who have rheumatic heart disease, bacteria may lodge on the heart valves or other parts of the endocardium, producing bacterial endocarditis. Transient bacteremia which may lead to bacterial endocarditis is known to occur following various surgical procedures including dental extractions and other dental manipulations which disturb the gums, the removal of tonsils and adenoids, the delivery of pregnant women, and operations on the gastrointestinal, genital, or urinary tracts. It is good medical and dental practice to protect patients with congenital heart disease by prophylactic measures.

Penicillin is the drug of choice for administration to patients with congenital heart disease undergoing dental manipulations or surgical procedures in the oral cavity. Although the exact dosage and duration of therapy are somewhat empirical, there is some evidence that for effective prophylaxis reasonably high concentrations of penicillin must be present at the time of the dental procedure. High levels of penicillin in the blood over a period of several days are recommended to prevent organisms from lodging on the endocardium during the period of transient bacteremia.

In general, the combined oral and parenteral route of administration is preferred. All patients should be instructed to report to their physician or clinic should they develop a fever within a month following the operation.

*First Choice—Intramuscular and Oral
Penicillin Combined*

For two days prior to surgery—200,000 to 250,000 units by mouth four times a day. On day of surgery—200,000 to 250,000 units by mouth four times a day and 600,000 units aqueous penicillin with 600,000 units procaine penicillin shortly before surgery. For two days thereafter—200,000 to 250,000 units by mouth four times a day.

*Second Choice (if injection is not feasible)—
Oral Penicillin*

200,000 to 250,000 units four times a day beginning two days prior to the surgical procedure and continued through the day of surgery or dental procedure and two days thereafter.

Contraindications

A history of sensitivity to penicillin.

Other Antibiotics

Erythromycin or the broad spectrum antibiotics should be employed as prophylaxis in patients who are sensitive to penicillin. In those who are undergoing surgery of the genitourinary or lower gastrointestinal tract, oxytetracycline or chlortetracycline should be administered in full dosage for five days, beginning treatment two days prior to the surgical procedure.

Protection against Respiratory Infections

Most children with cardiac defects tolerate infections (with the possible exception of pertussis) as well as other children. Patients with increased pulmonary flow or congestive failure, however, are very susceptible to respiratory infections. These patients may be greatly benefited by prolonged prophylactic use of chemotherapy or antibiotics during the younger years.

Attacks of Paroxysmal Dyspnea

Attacks of paroxysmal dyspnea are likely to occur in infants with defects which cause decreased pulmonary blood flow, such as tetralogy of Fallot. The attacks are due to anoxemia and not to heart failure.

The treatment for such an attack is:

Place the infant in knee-chest position.

Give morphine sulfate by hypodermic injection (1 mg. per 10 lb. body weight).

Give oxygen if available.

Attacks of paroxysmal tachycardia are an important indication for immediate cardiac evaluation.

Polycythemia

Polycythemia may occur in infants and is common in cyanotic children. A serious complication of polycythemia is cerebral thrombosis. As a preventive measure, the physician should prescribe an adequate fluid intake to avoid dehydration. After the first month of life, such infants require approximately one quart of fluid a day and should never be more than 8 to 10 hours without fluid even though it may be necessary to wake the infant. Children require about two quarts of fluid each 24 hours and should never be more than 12 hours without fluid. This fluid intake is especially important if the patient with polycythemia has fever, vomiting, or diarrhea, or is exposed to extreme heat.

Congestive Heart Failure

Congestive heart failure in infants and children, as in adults, requires rest, oxygen, and treatment with digitalis, morphine, and diuretics. The drugs should be given in dosages directly proportional to the body weight. If edema is present, the dosages should be based on normal body weight.

Cerebral Complications

The occurrence of cerebral thrombosis calls for immediate therapy. Oxygen therapy, venesection, fluid replacement, and other procedures may aid in lessening the extent of brain damage. Brain abscess in cyanotic children with cardiac malformations is frequent and calls for prompt treatment.

Paroxysmal Tachycardia

Paroxysmal tachycardia requires prompt therapy.

Jugular or abdominal pressure or breath holding may stop an attack. If these are un-

successful, digitalis is the drug of choice for infants and children. Great care and close observation, including frequent electrocardiograms, are advisable. Since episodes of atrial tachycardia have a marked tendency to recur in infancy, digitalis should be continued over a prolonged period of time.

Stridor

Stridor may be due to a vascular ring, a relatively rare congenital defect. During acute difficulty, hyperextension of the head and neck will often help. If choking occurs, the physician should be sure that the airway is clear. A moist atmosphere may also be helpful until the acute situation is relieved. Early surgery to correct the underlying condition is usually indicated.

Pregnancy

The therapy of pregnancy for the patient with a congenital cardiac defect begins before marriage. Many patients who survive to child-bearing age have anomalies that today are either curable or greatly ameliorated by surgical intervention. The pregnant woman with a congenital defect of the heart should be referred for evaluation at the earliest possible date. With the rapid advances in cardiac surgery today, sterilization of a young woman is seldom indicated.

With congenital defects, just as with acquired heart disease, the critical periods for development of heart failure parallel the periods of maximum load on the circulation. These critical periods are the seventh and eighth months of pregnancy, the later stages of labor, and the first postpartum days. Regardless of the type of underlying heart disease, a complete understanding of the functional capacity of the patient's heart is important, since it is the functional capacity which dictates the management of the pregnancy.³ Re-evaluation of the functional capacity at

each visit is necessary, because the status may change at any time during pregnancy.

Close observation of the patient during her pregnancy will help the physician predict the risk at the time of delivery and during the postpartum period. If the patient has not had any manifestations of clear-cut congestive failure prior to term, the maternal mortality is between 1 and 2 per cent; if prior to term she has developed failure which responded to treatment, the risk is considerably increased (about 40 per cent); if congestive failure is present at the time of delivery, maternal mortality is high (about 40 per cent).

Unless there are obstetrical reasons for it, Cesarean section is generally contraindicated in patients with any type of heart disease. The possible exception is coarctation of the aorta, where there is risk of a vascular accident.^{4, 5}

A woman with a congenital cardiovascular defect has a slightly greater chance of having a child with a congenital abnormality. This chance is so slight, however, that it should not be considered a contraindication to pregnancy.

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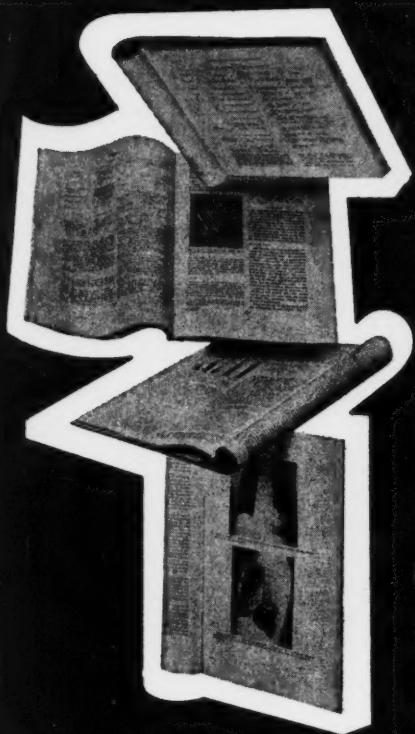
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